Pergamon

Tetrahedron Letters 39 (1998) 5517–5520

TETRAHEDRON LETTERS

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

Kazuhiro Haraguchi, Motoi Hosoe, Hiromichi Tanaka,* Sayo Tsuruoka, Kazuhiro Kanmuri, and Tadashi Miyasaka*

School of Pharmaceutical Sciences, Showa University, Hatanodai 1-5-8, Shinagawa-ku, Tokyo 142-8555, Japan

Received 22 April 1998; revised 19 May 1998; accepted 22 May 1998

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) *S*N2 reaction (intramolecular Williamson reaction),[2a),2b),2d)] 2) 6-*exo-trig* oxymercuration,[2e)] 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.

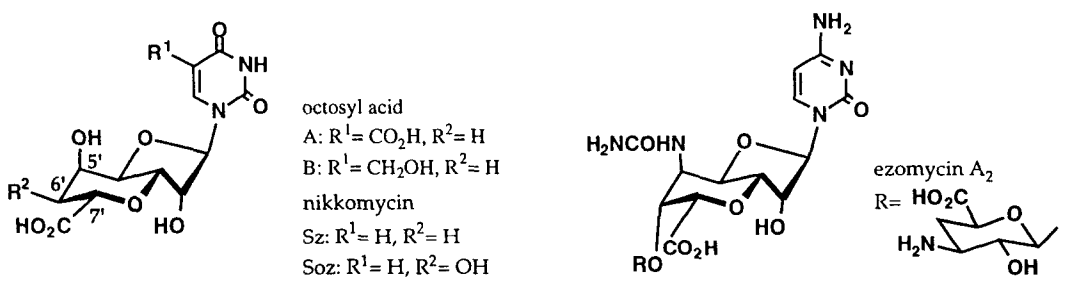
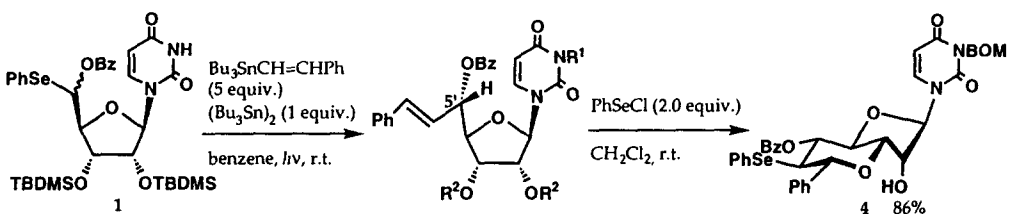


Fig. 1

0040-4039/98/$19.00
PII: S0040-4039(98)01087-9

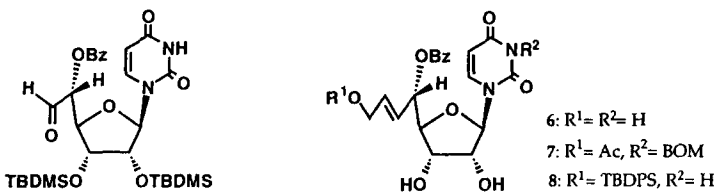
As we have already reported, the uridine 5'-monoselenoacetal **1** reacts with various types of radical acceptors to provide a stereoselective C-C bond formation at the 5'-position.[4] When styryltributylstannane was used as the radical acceptor, the (5'*S*)-*C*-styryl derivative **2** was obtained in 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]

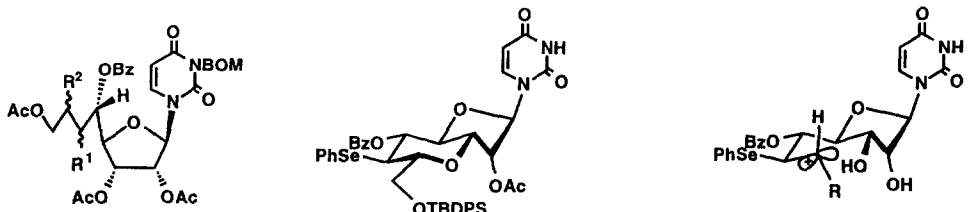
As the first substrate for cyclization, we selected the allyl alcohols **7** and **8**. Compounds **7** and **8** were prepared as follows: oxidative cleavage of the styryl moiety of **2** with $NaIO_4$-OsO_4 to give the aldehyde **5** (quant.); the Wittig reaction of **5** with Ph_3P=CHCHO followed 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

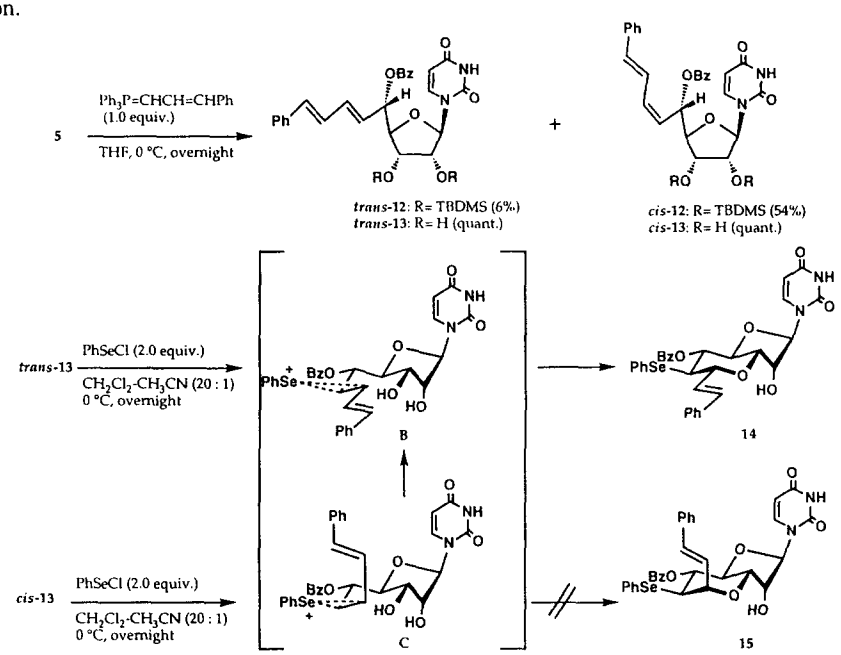




Scheme 2

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.

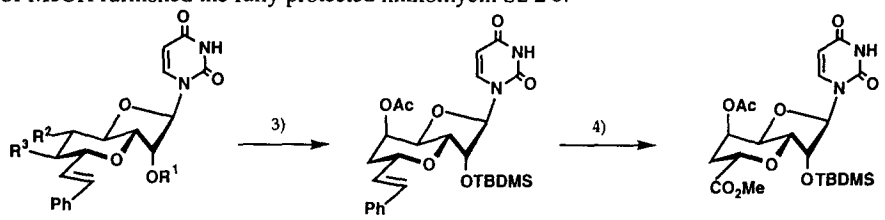
The conjugate diene **13** was prepared as shown in Scheme 3. Thus, Wittig reaction of the aldehyde **5** with Ph_3P=CHCH=CHPh in THF at 0 ℃ gave a mixture of *trans*-**12** (6%) and *cis*-**12** (54%), each of which was isolated by HPLC. Desilylation of **12** led to the precursor *trans*-**13** and *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 } 1)
18: R^1= TBDMS, R^2= OH, R^3= H } 2)

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.

Acknowledgement. Financial support from the Ministry of Education, Science, Sports and Culture (Grant-in-Aid No. 09771922 to K.H.) is gratefully acknowledged.

REFERENCES AND NOTES

1) (a) Isono, K. *J. Antibiot.* **1988**, *41*, 1711-1739. (b) Isono, K. *Pharmacol. Ther.* **1991**, *52*, 269-286.

2) (a) Kim, K. S.; Szarek, W. A. *Can. J. Chem.* **1981**, *59*, 878-888. (b) Sakanaka, O.; Ohmori, T.; Kozaki, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3523-3528. (c) Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *Tetrahedron Lett.* **1989**, *30*, 2829-2832. (d) Danishefsky, S.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486-2487. (e) Hanessian, S.; Kloss, J.; Sugawara, T. *J. Am. Chem. Soc.* **1986**, *108*, 2758-2759.

3) Alternative synthetic methods, which are based on construction of a five-membered cyclic ether on a hexopyranose skeleton, have been also reported. (a) Maier, S.; Preuss, R.; Schmidt, R. R. *Liebigs Ann. Chem.* **1990**, 483-489. (b) Knapp, S.; Shieh, W.-C.; Jaramillo, C.; Trilles, R. V.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 946-948.

4) (a) Haraguchi, K.; Tanaka, H.; Saito, S.; Yamaguchi, K.; Miyasaka, T. *Tetrahedron Lett.* **1994**, *35*, 9721-9724. (b) Haraguchi, K.; Tanaka, H.; Saito, S.; Kinoshima, S.; Hosoe, M.; Kanmuri, K.; Yamaguchi, K.; Miyasaka, T. *Tetrahedron* **1996**, *52*, 9469-9484.

5) Synthetic methods for oxidative transformation of aromatic or heteroaromatic rings into carboxylic acid derivatives have been reported. However, pyrimidine nucleosides have been reported to be unstable under the oxidative conditions. See: Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. *J. Org. Chem.* **1997**, *62*, 5497-5507.

6) Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett.* **1996**, *34*, 6145-6148.