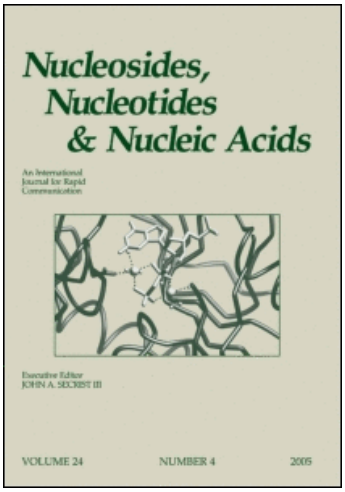


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Unusual Olefin Formation by PhSe-F *trans*-Elimination

Jinfa Du[a]; Junxing Shi[a]; Byoung-Kwon Chun[a]; Ann Hobbs[a]; Laurent Hollecker[a]; Kyoichi A. Watanabe[a]
[a] Pharmasset, Inc., Tucker, Georgia, USA

To cite this Article Du, Jinfa , Shi, Junxing , Chun, Byoung-Kwon , Hobbs, Ann , Hollecker, Laurent and Watanabe, Kyoichi A.(2005) 'Unusual Olefin Formation by PhSe-F *trans*-Elimination', Nucleosides, Nucleotides and Nucleic Acids, 24: 9, 1289 — 1292
To link to this Article: DOI: 10.1080/15257770500230335
URL: http://dx.doi.org/10.1080/15257770500230335

Nucleosides, Nucleotides, and Nucleic Acids, 24 (9):1289–1292, (2005)

ISSN: 1525-7770 print/ 1532-2335 online
DOI: 10.1080/15257770500230335

Taylor & Francis
Taylor & Francis Group

UNUSUAL OLEFIN FORMATION BY PhSe-F *TRANS*-ELIMINATION

Jinfa Du, Junxing Shi, Byoung-Kwon Chun, Ann Hobbs, Laurent Hollecker, and Kyoichi A. Watanabe □ *Pharmasset, Inc., Tucker, Georgia, USA*

□ *A new approach to the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides was described in excellent yield through unusual olefin formation by PhSe-F trans-elimination.*

Keywords Nucleoside, HBV, HIV, Elimination

INTRODUCTION

Several 2′,3′-didehydro-2′,3′-dideoxynucleosides (d4-nucleosides) showed potent activity against human immunodeficiency virus (HIV) in vitro.[1] D-2′,3′-Didehydro-3′-deoxythymidine (d4T) has been approved by the FDA for clinical treatment of HIV infection.[2] D-2′,3′-Didehydro-2′,3′-dideoxy-5-fluorocytidine (d4FC) is currently in Phase II evaluation for the clinical treatment of HIV infection, which is resistant to other nucleoside drugs, such as AZT and 3TC.[3] Recently, L-2′,3′-didehydro-2′,3′-dideoxy-3′-fluorocytidine (L-3′-Fd4C) was reported to show promising antiviral activity against HIV infection.[4] Due to the importance of d4-nucleosides in antiviral chemotherapy, there are several methods developed for the syntheses of d4-nucleosides.[5–9] Mattock's bromide, 2-acetoxyisobutyryl bromide, made the synthesis of d4-nucleosides from *ribo*-nucleosides practical.[9] d4-Nucleosides can be prepared in excellent yields by the treatment of *ribo*-nucleosides with Mattock's bromide followed by reductive-elimination with Cu-Zn and deprotection. We herein report a new approach to the synthesis of d4-nucleosides in excellent yield by the treatment of 2,2′-anhydro-3′-fluorolyxofuranosyl nucleoside with lithium phenylselenide (LiSePh).

In our ongoing drug development program, a sufficient amount of L-3′-Fd4C was needed for in vivo evaluation. The original method from L-arabinose in 13 steps gave very low overall yield (3.88%).[4] Therefore, it was necessary for us to develop a novel procedure scalable for its preparation in a large quantity. Huang

Received 13 January 2005, accepted 2 May 2005.
Address correspondence to Dr. Jinfa Du, Pharmasset, Inc., 1860 Montreal Road, Tucker, GA 30084, USA; Fax: (678) 395-0030; E-mail: jdu@pharmasset.com

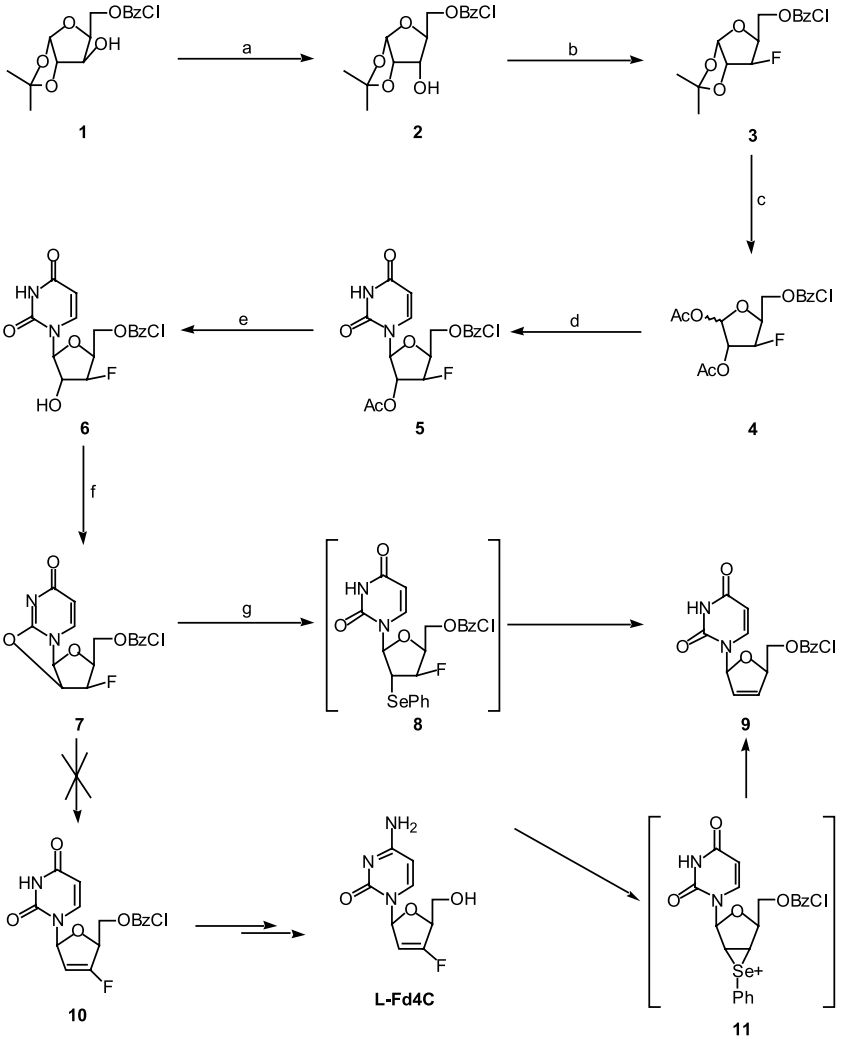
et al. reported that D-2′,3′-didehydro-3′-deoxy-2′-fluorothymidine (2′-Fd4T) was synthesized from 2,3′-anhydro-2′-deoxy-2′-fluorolyxofuranosyl-5-methyluracil in excellent overall yield by elimination catalyzed by *t*-BuOK in dimethylsulfoxide (DMSO).[10] This strategy was utilized to explore the synthesis of L-3′-Fd4C through the similar elimination of the key intermediate, 2,2′-anhydro-nucleoside **7**.

RESULTS AND DISCUSSION

The exploration for the preparation of L-3′-Fd4C was illustrated in Scheme 1. Compound **1** was prepared by Nomura's method[11] for its D-isomer. Oxidation of compound **1** with NaOCl catalyzed by 2,2,6,6-tetramethyl-1-piperidinyoxy (TEMPO) followed by reduction of the resulting ketone with $NaBH_4$ gave the *ribo*-sugar **2** in excellent yield.[11,12] Treatment of **2** with (diethylamino)sulfur trifluoride (DAST) in methylene chloride afforded the fluoro-sugar **3** in 80% yield.[13] Acetolysis of compound **3** in Ac_2O/AcOH in the presence of H_2SO_4 followed by coupling with silylated uracil in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided β-nucleoside **5** in good yield.[14] Deacetylation of **5** with Et_3N in MeOH produced 1-(3′-deoxy-3′-fluoro-L-xylofuranosyl)uracil derivative **6** in moderate yield. The key intermediate 3′-deoxy-3′-fluoro-2,2′-anhydronucleoside **7*** was obtained by reaction of compound **6** with mesyl chloride in the presence of Et_3N followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at reflux in methylene chloride. In contrast to the preparation of 2′-F-d4T, complete decomposition was observed when compound **7** was treated with *t*-BuOK in DMSO.[10] It was reported that d4-nucleosides could be prepared by the treatment of 2,2′-anhydro-nucleosides with phenylselenide ion followed by oxidative elimination of the resulting 2′-phenylselenonyl intermediate with hydrogen peroxide.[15–17] In order to prepare 2′-phenylselenonyl intermediate **8**, which could be further converted to intermediate **10** for L-3′Fd4C by oxidative elimination with H_2O_2, compound **7** was treated with lithium phenylselenide (LiSePh) in tetrahydrofuran (THF) at reflux temperature. Instead of the expected **8**, 5′-*O*-(*p*-chlorobenzoyl)-β-L-2′,3′-didehydro-2′,3′-dideoxyuridine (**9**)† was obtained in 86% yield. The structures of **7** and **9** were determined by high-resolution mass spectroscopy (HRMS) and comparison of ^{1}H-NMR data with that reported in literature.[5]

*Compound **7**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 8.4 Hz, 2H, 2Bz-H), 7.90 (d, J = 7.2 Hz, 1H, H-6), 7.62 (d, J = 8.4 Hz, 2H, 2Bz-H), 6.20 (d, J = 6.0 Hz, 1H, H-1′), 5.88 (d, J = 8.0 Hz, 1H, H-5), 5.72 (m, 1H, H-2′), 5.61 (dm, J = 56.0 Hz, 1H, H-3′), 4.65 (m, 1H, H-4′), 5.59 (dd, J = 4.4, 12.0 Hz, 1H, H-5′), 4.40 (dd, J = 8.0, 12.0 Hz, 1H, H-5″). Anal Calcd for $C_{16}H_{12}ClFN_2O_5$: C, 52.40; H, 3.30; N, 7.64. Found: C, 52.19; H, 3.35; N, 7.65.

†Compound **9**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.40 (s, 1H, D_2O exchangeable, NH), 7.94 (d, J = 8.0 Hz, 2H, 2Bz-H), 7.64 (d, J = 6.8 Hz, 2H, 2Bz-H), 7.34 (d, J = 8.8 Hz, 1H, H-6), 6.82 (m, 1H, H-1′), 6.53 (d, J = 6.0 Hz, 1H, H-3′), 6.05 (d, J = 6.0 Hz, 1H, H-2′), 5.28 (d, J = 8.4 Hz, 1H, H-5), 5.12 (br s, 1H, H-4′), 4.55 (dd, J = 3.2, 12.0 Hz, 1H, H-5′), 4.45 (dd, J = 5.2, 12.0 Hz). Anal Calcd for $C_{16}H_{13}ClN_2O_5 \cdot 1/4H_2O$: C, 54.35; H, 3.75; N, 7.92. Found: C, 54.31; H, 3.81; N, 7.85.



SCHEME 1 Reagents and conditions: a) i. TEMPO, NaOCl, H_2O; ii. $NaBH_4$; b) DAST, CH_2Cl_2; c) Ac_2O, AcOH, H_2SO_4; d) silylated uracil, TMSOTf, CH_2Cl_2; e) Et_3N, MeOH; f) i. MsCl, Et_3N, CH_2Cl_2; ii. DBU, CH_2Cl_2; g) $(PhSe)_2$, $LiBH_4$, EtOH.

Possible mechanism of generation of compound **9** was also illustrated in Scheme 1. Phenylselenide ion might attack the 2′-position of compound **7** to produce an intermediate **8**, which could be converted to d4-nucleoside **9** by the direct *trans*-elimination of F-Se or through intermediate **11**. Our observation is unique because fluorine is not considered a leaving group in the aliphatic system.[10,18]

In conclusion, a new approach to the synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides has been developed in excellent yield by the treatment of 2,2′-anydro-3′-deoxy-3′-fluorolyxofuranosyl nucleoside with lithium phenylselenide through a quite unusual mechanism.

REFERENCES

1. Zemlicka, J. Enantioselectivity of the antiviral effects of nucleoside analogues. Pharmacol. Ther. **2000**, *85*, 251–266.
2. Lin, T.-S.; Schinazi, R.F.; Prusoff, W.H. Potent and selective in vitro activity of 3′-deoxythymidin-2′-ene (3′-deoxy-2′,3′-didehydrothymidine) against human immunodeficiency virus. Biochem. Pharmacol. **1987**, *36*, 2713–2718.
3. Ma, L.; Hurwitz, S.J.; Shi, J.; McAree, J.J.; Liotta, D.C.; McClure, H.M.; Schinazi, R.F. Pharmacokinetics of the antiviral agent β-D-2′,3′-didehydro-2′,3′-dideoxy-5-fluorocytidine in rhesus monkeys. Antimicrob. Agents Chemother. **1999**, *43*, 381–384.
4. Chong, Y.; Gumina, G.; Mathew, J.S.; Schinazi, R.F.; Chu, C.K. L-2′,3′-Didehydro-2′,3′-dideoxy-3′-fluoronucleosides: synthesis, anti-HIV activity, chemical and enzymatic stability, and mechanism of resistance. J. Med. Chem. **2003**, *46*, 3245–3256.
5. Beach, J.W.; Kim, H.O.; Jeong, L.S.; Nampalli, S.; Islam, Q.; Ahn, S.K.; Babu, J.R.; Chu, C.K. A highly stereoselective synthesis of anti-HIV 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides. J. Org. Chem. **1992**, *57*, 3887–3894.
6. Ando, M.; Ohhara, H.; Takase, K. A mild and stereospecific conversion of vicinal diols into olefins via 2-methoxy-1,3-dioxolane. Chem. Lett. **1986**, 879–882.
7. Clive, D.L.J.; Sgarbi, P.W.M.; Wickens, P.L. Synthesis of 2′,3′-didehydro-2′,3′-dideoxynucleosides by reaction of 5′-*O*-protected nucleoside 2′,3′-dimesylates with lithium areneselenolates. J. Org. Chem. **1997**, *62*, 3751–3753.
8. Lin, T.-S.; Luo, M.-Z.; Liu, M.-C.; Zhu, Y.-L.; Gullen, E.; Dutschman, G.E.; Cheng, Y.-C. Design and synthesis of 2′,3′-dideoxy-2′,3′-didehydro-β-L-cytidine (β-L-d4C) and 2′,3′-dideoxy-2′,3′-didehydro-β-L-5-fluorocytidine (β-L-Fd4C), two exceptionally potent inhibitors of human hepatitis B virus (HBV) and potent inhibitors of human immunodeficiency virus (HIV) in vitro. J. Med. Chem. **1996**, *39*, 1757–1759.
9. Greenberg, S.; Moffatt, J.G. Reactions of 2-acyloxyisobutyryl halides with nucleosides. I. Reactions of model diols and of uridine. J. Am. Chem. Soc. **1973**, *95*, 4016–4024.
10. Huang, J.-Y.; Chen, L.-C.; Wang, L.; Kim, M.-H.; Warshaw, J.A.; Armstong, D.; Zhu, Q.-Y.; Chou, T.-C.; Watanabe, K.A.; Matulic-Adamic, J.; Su, T.-L.; Fox, J.J.; Polsky, B.; Baron, P.A.; Gold, J.W.M.; Hardy, W.D.; Zuckerman, E. Fluorinated sugar analogs of potential anti-HIV-1 nucleosides. J. Med. Chem. **1991**, *34*, 1640–1646.
11. Nomura, M.; Sato, T.; Washnosu, M.; Tanaka, M.; Asao, T.; Shuto, S.; Matsuda, A. Nucleosides and nucleotides. Part 212: practical large-scale synthesis of 1-(3-*C*-ethynyl-beta-D-*ribo*-pentofuranosyl)cytosine (ECyd), a potent antitumor nucleoside. Isobutyryloxy group as an efficient anomeric leaving group in the Vorbruggen glycosylation reaction. Tetrahedron **2002**, *58*, 1279–1288.
12. Ma, T.; Pai, S.B.; Zhu, Y.L.; Lin, J.S.; Shanmuganathan, K.; Du, J.; Wang, C.; Kim, H.; Newton, G.M.; Cheng, Y.-C.; Chu, C.K. Structure-activity relationships of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides as anti-hepatitis B virus agents. J. Med. Chem. **1996**, *39*, 2835–2843.
13. Gudmundsson, K.S.; Freeman, G.A.; Drach, J.C.; Townsend, L.B. Synthesis of fluorosugar analogues of 2,5,6-trichloro-1-(β-D-ribofuranosyl)benzimidazole as antivirals with potentially increased glycosidic bond stability. J. Med. Chem. **2000**, *43*, 2473–2478.
14. Du, J.; Surzhykov, S.; Lin, J.S.; Newton, M.G.; Cheng, Y.-C.; Schinazi, R.F.; Chu, C.K. Synthesis, anti-human immunodeficiency virus and anti-hepatitis B virus activities of novel oxaselenolane nucleosides. J. Med. Chem. **1997**, *40*, 2991–2993.
15. Haraguchi, K.; Tanaka, H.; Maeda, H.; Itoh, Y.; Saito, S.; Miyasaka, T. Selenoxide elimination for the synthesis of unsaturated-sugar uracil nucleosides. J. Org. Chem. **1991**, *56*, 5401–5408.
16. Tong, W.; Xi, Z.; Gioeli, C.; Chattopadhyaya, J. Synthesis of new 2′,3′-modified uridine derivatives from 2′,3′-ene-2′-phenylselenonyl uridine by michael addition reactions. Tetrahedron **1991**, *47*, 3431–3450.
17. Beach, J.W.; Kim, H.O.; Jeong, L.S.; Nampalli, S.; Islam, Q.; Ahn, S.K.; Babu, J.R.; Chu, C.K. A highly stereoselective synthesis of anti-HIV 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides. J. Org. Chem. **1992**, *57*, 3887–3894.
18. Siddiqui, M.A.; Driscoll, J.S.; Abushanab, E.; Kelley, J.A.; Barchi, J.J., Jr.; Marquez, V.E. The "β-fluorine effect" in the non-metal hydride radical deoxygenation of fluorine-containing nucleoside xanthates. Nucleosides Nucleotides Nucleic Acids **2000**, *19*, 1–12.