Pergamon

Tetrahedron Letters, Vol. 37, No. 25, pp. 4297-4300, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00829-5

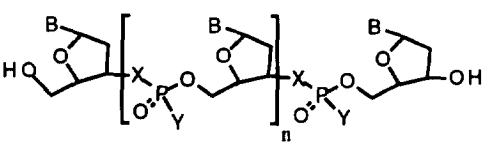
PREPARATION OF 3'-PHOSPHONATE ANALOGS OF 2',3'-DIDEOXYNUCLEOSIDES

Wai Y. Lau, Lihua Zhang,[a] Jianwu Wang,[b] Dongliang Cheng,[c] and Kang Zhao*

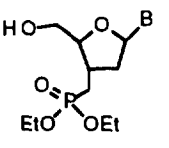
Department of Chemistry, 29 Washington Place, New York University,
New York, NY 10003

Summary: γ-Hydroxyl vinylphosphonate (**6**) has been efficiently prepared by the base-catalyzed opening of the readily available epoxide (**5**) and converted to the corresponding nucleosides for antiviral studies.

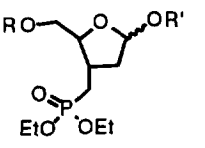
Nucleoside isosteric phosphonates (**1**) have been recently considered as possible alternatives for oligodeoxynucleosides as antisense agents (Scheme 1).[1] The oligomers (**1a**, X = CH_2, Y = O^-) based on phosphonate bond do not introduce new asymmetric centers, and are expected to resist nucleases due to the partial modification of natural phosphate bond.[1] However, antisense properties of the oligomers (**1a** , X = CH_2, Y = O^-) have not been studied owing to a lack of readily available starting materials.[2] Phosphonates (**2**) can serve as useful building blocks for the preparation of compounds (**1a**). The potential value of nucleoside phosphonates (**2**) has prompted us to design a synthesis for a key intermediate such as phosphonate (**3**), which could lead to either the corresponding nucleotide oligomers (**1**)[3] or the nucleoside analogs (**2**) for antiviral studies.[4] Herein, we describe a strategy for the construction of optically active compounds (**2**) via the phosphonate intermediate (**3**).[5]



1



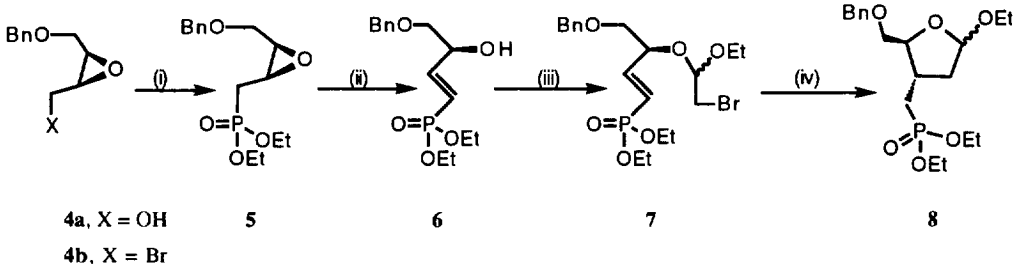
2



3

Scheme 1

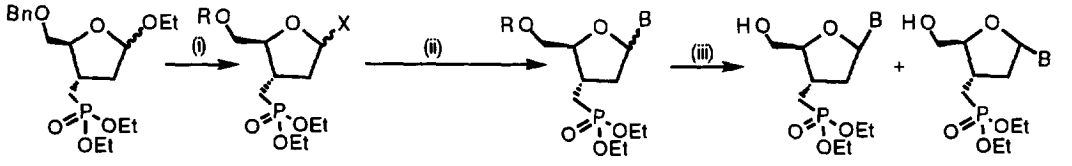
Central to this synthetic strategy are base-catalyzed opening of a chiral epoxide and furan ring formation via the radical cyclization[6] of a vinylphosphonate (Scheme 2). Compound (**4a**) was prepared according to a literature procedure[7] and was converted to the corresponding bromide (**4b**) in 89% yield. Although the Arbusov reaction of (**4b**) with trimethyl phosphite was not successful due to the rapid conversion of phosphite to dimethyl methylphosphonate, the use of neat triethyl phosphite produced the desired product (**5**) in 95% yield. The reaction of 10 grams of β,γ-epoxyphosphonate (**5**) with a catalytic amount of sodium ethoxide (0.1 eq.) in 100 ml of ethanol opened the epoxide within one hour to give the *trans* vinylphosphonate (**6**) in 96% yield. Treatment of (**6**) with the bromoacetal reagent,[6a] prepared from bromine and ethylvinyl ether, formed bromide (**7**) which upon radical-cyclization afforded (**8**) as a mixture of two diastereomeric products. The stereochemistry of these two products was ascertained to be *trans* 3,4-disubstituted, regardless of the stereochemistry of 1-ethoxyl stereocenter.[5b,6b] The approach described here is concise and all of the five reactions, including the epoxide-ring opening, the Arbusov condensation, and the Stork cyclization, were also carried out in a large scale resulting in high yields.



Scheme 2: (i) CBr_4, Ph_3P, MeCN, 0 °C to r t, 2 h, 89%; then $P(OEt)_3$, 140 °C, 7 h, 95%. (ii) EtONa (0.1 eq.), EtOH, rt, 1 h, 96%. (iii) Br_2, ethylvinyl ether, Et_2O, -78 °C, then (**6**), Et_3N, rt, 7 h, 74%. (iv) *n*-Bu_3SnH, AIBN, PhH, 78 °C, 6 h, 88%.

The preparation of nucleoside anologs (**2**) was investigated using different starting materials (**9a-c**) and under various reaction conditions (Scheme 3). The coupling intermediate (**9a**) can be prepared either by PPTS-catalyzed hydrolysis of acetal (**8**), followed by acetylation, or by direct hydrolysis of (**8**) in the presence of acetic acid and anhydride. The other coupling intermediates (**9b**)[8] and (**9c**) are also easily accessible as shown in Scheme 3. The coupling of (**9a-c**) with trimethylsilylated thymine gave the corresponding phosphonates in good yields, but the α/β selectivity varied between 3:1 to 1:6. Although a continued investigation is required to study the effect of the R group of (**9**) on the resultant stereochemistry of nucleoside-base

coupling, the present method provides both isomers for their antiviral activity studies. The preparation of other analogs containing different nucleoside bases and their anti-HIV activity studies are currently in progress.



8 **9a**, R = Bn, X = OAc; **9b**, R = Bn, X = SPh; **9c**, R = Ac, X = OAc **10a**, R = Bn; **10b**, R = Ac **2** **11**

Scheme 3. (i) (**8**) to (**9a**): AcOH, Ac_2O, CSA, 70 °C, 0.5 h, 70%; (**9a**) to (**9b**): PhSSiMe, ZnI_2, $(ClCH_2)_2$, rt, 2 h, 74%; (**9a**) to (**9c**): EtOAc, Pd/C, H_2, rt, 0.5 h, 71%, then Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 73%. (ii) Bis(TMS) thymine, $(ClCH_2)_2$; (**9a**) to (**10a**): $SnCl_4$, 2 h, rt, 55%, α:β = 3:1; (**9b**) to (**10a**): NBS, CH_2Cl_2, -78 °C, 1 h, 80%, α:β = 1:2; (**9c**) to (**10b**): BF_3 OEt_2, rt, 2 h, 87%, α:β = 1:6; (iii) For (**10a**), Pd/C, H_2, rt, 1 h, 70%; for (**10b**), K_2CO_3, MeOH, 2 h, 80%.

In conclusion, a very simple and concise approach provides the optically active phosphonate (**8**) in a large quantity which can be converted to phosphonate nucleoside analogs (**2**) and (**11**). Meanwhile, the monomers (**2**) will be used in their insertion into oligodeoxynucleosides to yield substrates such as (**1**), which can be used in testing their resistances to nucleases.

Acknowledgment: We thank Jie Chen for his technical assistance and the American Cancer Society, the NSF Faculty Early Career Development Program, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support.

[a,b,c] Present addresses:
(a) The University of Pennsylvania, Department of Chemistry, PA 16802.
(b) Peptosyn Inc. 86, Yonkers Ave. Tuckahoe, NY 10707.
(c) Department of Chemistry, Lanzhou University, Lanzhou 73000 PRC.

References:

1. For selected reviews, see: (a) Zon, G. *Pharmaceutic. Research* **1988**, *5*, 539. (b) van der Krol, A. R. Mol, J. N. M. Stuitje, A. R. *Biotechniques*, **1988**, *6*, 958. (c)

Weintraub, H. M. *Scientific American*, **1990**, 40. (d) Uhlmann, E. Peyman, A. *Chemical Reviews*, **1990**, *90*, 543. (e) Moffat, A. S. *Science*, **1991**, *253*, 510. (f) Milligan, J. F.; Matteucci, M. D.; Martin, J. C. *J. Med. Chem.* **1993**, *36*, 1923.

2. (a) Albrecht, H. P.; Jones, G. H.; Moffatt, J. G. *Tetrahedron* **1984**, *40*, 79 and references therein. (b) Morr, M.; Ernst, L. *Liebigs Ann. Chem.* **1993**, 1205 and references therein.
3. A method for the preparation of mixed phosphonate esters has been reported, see: Zhao, K.; Landry, D. W. *Tetrahedron*, **1993**, *49*, 363.
4. Development of new antiviral agents is an ongoing program in our laboratory and, for our publications, see: (a) Xiang, Y.; Chen, J.; Schinazi, R. F.; Zhao, K. *Tetrahedron Lett.* **1995**, *36*, 7193. (b) Xiang, Y.; Chen, J.; Schinazi, R. F.; Zhao, K. *Bioorg. Med. Chem. Lett.* **1996**, in press.
5. Two efficient procedures for the preparation of (**3**) have recently been disclosed. (a) Pragnaacharyulu, P. V. P.; Abushanab, E. *Tetrahedron Lett.* **1995**, *36*, 5507. (b) Yokomatsu, T.; Shimizu, T.; Yuasa, Y.; Shibuya, S. *Synlett* **1995**, 1280.
6. (a) Stork, G.; Mook, R. Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (b) Lavallee, J. F.; Just, G. *Tetrahedron Lett.* **1991**, *32*. 3469.
7. Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
8. Hanessian, S.; Guindon, Y. *Carbohydr. Res.* **1980**, *86*, C3.

(*Received in USA* 15 *February* 1996; *revised* 18 *April* 1996; *accepted* 25 *April* 1996)