European Journal of Medicinal Chemistry 150 (2018) 642–654

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Synthesis of 3′-halo-5′-norcarbocyclic nucleoside phosphonates as potent anti-HIV agents

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ARTICLE INFO

Article history:
Received 19 February 2018
Received in revised form
9 March 2018
Accepted 13 March 2018
Available online 14 March 2018

Dedicated to Dr. Gilles Gosselin at the occasion of his retirement and his outstanding career in the field of nucleoside analogues as antiviral agents

Keywords:
Antiviral
HIV
Nucleoside analogues
Carbocycle
Phosphonates

ABSTRACT

The synthesis and the antiviral evaluation of 3'-halo (iodo and fluoro) 5'-norcarbocyclic nucleoside phosphonates is described. No antiviral activity was observed against Zika virus, Dengue virus 2, HSV-1, HSV-2 and Chikungunya virus. In contrast, some of the synthesized compounds are potent inhibitors of the replication of HIV-1, comparatively to (*R*)-PMPA, with no concomitant cytotoxicity.

1. Introduction

More than three decades after the discovery of the Human Immunodeficiency Virus (HIV) as the etiologic agent of AIDS, there is no vaccine available for the prevention of AIDS and drugs are the only arsenal to treat HIV infections [1,2]. However, current treatments do not allow the eradication of the virus but contain its replication at undetectable level with the obligation for the infected individuals to stay on treatment for life. This is a crucial issue because all existing *anti*-HIV drugs have long-term side effects and may be associated with the rapid emergence of resistant viral strains in case of faulty observance to treatment or suboptimal treatment. These concerns still promote the research for novel molecular-based *anti*-HIV drugs. Among these later, nucleoside and nucleotide analogues are an important class of *anti*-HIV drugs [3] as illustrated with the clinical use of Abacavir, a carbocyclic nucleoside analogue, and Tenofovir disoproxil fumarate (TDF), the corresponding carbonate prodrug of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (*R*-PMPA, Tenofovir), an acyclonucleoside phosphonate (Fig. 1).

In the case of carbocyclic nucleosides, such as Abacavir, the replacement of the endocyclic oxygen of the furanose ring by a methylene group confers chemical and metabolic stabilities. In the case of nucleoside phosphonates, such as Tenofovir, the presence of P-C bond instead of the hydrolysable P-O brings about a metabolic stability of the linkage with the phosphate moiety. As a part of our research on 5′-norcarbocyclic nucleoside phosphonates as potential anti-viral agents [4], we describe here the synthesis and the antiviral evaluation of their 3′-halo (iodo and fluoro) corresponding counterparts bearing purine bases.

2. Results and discussion

2.1. Chemistry

The strategy for the synthesis of 3′-halo-5′-norcarbocyclic nucleoside phosphonates was based upon the preparation of compound (±) **6** as a common precursor (Scheme 1). Furfuryl alcohol was used as starting material and provided carbocycle (±) **1**

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https://doi.org/10.1016/j.ejmech.2018.03.038
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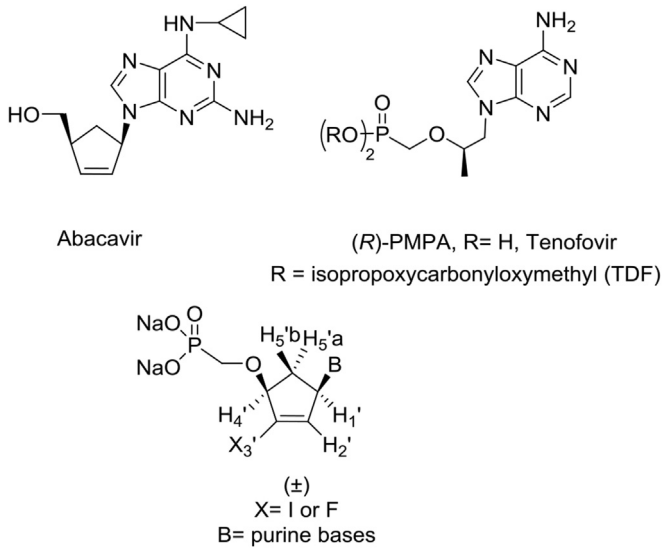


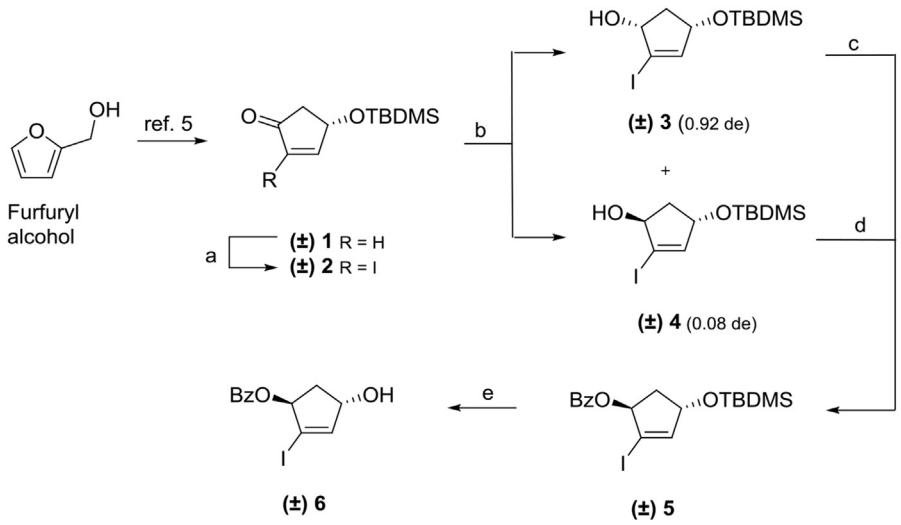
Fig. 1. Examples of *anti*-HIV carbocyclic nucleosides and acyclonucleoside phosphonates. Structures and numbering of the target 5′-norcarbonucleoside phosphonate analogues.

according to the procedure described by Curran [5]. The iodination reaction on compound (±) **1** was attempted according to the procedure described by Johnson (2 eq. of iodine in pyridine/CCl_4) [6,7]. Nevertheless, the moderate yield obtained (61%) prompted us to achieve the iodination reaction in the presence of pyridinium dichromate as a catalyst [8] and afforded α-iodinated enone (±) **2** in 86% yield. Reduction of the ketone under Luche conditions [9,10] gave a mixture of diastereoisomers (±) **3** and (±) **4**. These compounds were easily separated by purification on silica gel column chromatography and the diastereoisomers (±) **3** and (±) **4** (92/8 ratio) were isolated in 93% yield. From (±) **3**, a Mitsunobu reaction [11] in the presence of benzoic acid, PPh_3, and DIAD or a direct benzoylation of (±) **4** provided carbocyclic (±) **5** in 98% and 75% yield, respectively. Finally, the removal of the TBDMS protecting group in the presence of TBAF afforded the desired common precursor (±) **6** in 95% yield.

Synthesis of 3′-iodo-5′-norcarbocyclic nucleoside phosphonates bearing adenine, *N*-cyclopropyl-6-aminopurine, hypoxanthine and guanine (respectively compounds (±) **12**, (±) (**15**), (±) **18** and (±) (**20**) is described in Scheme 2.

Starting with a Mitsunobu coupling reaction between alcohol (±) **6** and an appropriate heterocyclic base, the *N9*-carbocyclic nucleosides were obtained without concomitant formation of the *N7* regioisomer [12]. Compound (±) **7**, a common intermediate for the synthesis of the target compounds (±) **12**, (±) (**15**) and (±) **18**, was obtained using 6-chloropurine as heterocyclic base whereas 2-amino-6-chloropurine was used to provide carbocyclic nucleoside (±) **8**, precursor of the target compound (±) **20**. The stereochemical assignments of compound (±) **7** were achieved through NMR experiments (Fig. 2). A NOE correlation between protons H1′ and H4′ was observed and support the *cis* orientation of these protons. These data were in agreement with our previous results on 3′-methyl-5′-norcarbocyclic nucleoside phosphonates [4] and confirm the stereochemistry obtained under Mitsunobu reaction.

Treatment of compound (±) **7** in the presence of methanolic ammonia gave the adenine derivative (±) **9** in 81% yield. Protection of the amino group as a *N,N*-dimethylformamidine [13] in order to avoid competing N-alkylation led to compound (±) **10** in 93% yield. *O*-Alkylation of (±) **10** in the presence of Li*Ot*Bu and diethyl *p*-toluene sulfonyloxymethyl phosphonate [14], followed by an acidic treatment, afforded carbocyclic nucleoside (±) **11** in 73% yield. Finally, the target nucleotide (±) **11** was obtained in 73% yield by deprotection of the phosphonate group in the presence of TMSBr in DMF. Concomitantly, nucleophilic substitution of compound (±) **7** with cyclopropylamine followed by removal of the benzoate group under basic conditions led readily to nucleoside (±) **13**. Condensation of the phosphonate group with carbocycle (±) **13** followed by the hydrolysis of the diethyl phosphonate esters was performed using as previously for (±) **12**. The phosphonic acid was then subject to an ion exchange chromatography to yield the target 3′-iodo-5′-norcarbocyclic nucleoside phosphonate (±) **15** as sodium salt. Then, we planned the synthesis of the derivative (±) **18** bearing hypoxanthine as nucleobase. In this respect, treatment of (±) **7** with potassium carbonate in methanol allowed the nucleophilic substitution of the chlorine atom and hydrolysis of the benzoate group to afford carbocyclic nucleoside (±) **16** in good yield. Condensation of the phosphonate group led to compound (±) **17** and removal of the diethyl phospho esters accompanied by the concomitant hydrolysis of the methoxy group in position 6 [4] gave the target



Scheme 1. Synthesis of carbocycle (±) **6**. Reagents and conditions: (a) I_2, PDC, CH_2Cl_2, rt, 46 h, 86%; (b) $CeCl_3$, $NaBH_4$, CH_3OH, −78 °C, 2 h, 93%; (c) benzoic acid, PPh_3, DIAD, THF, 0 °C, 1 h, 98%; (d) BzCl, pyridine/CH_2Cl_2, CH_2Cl_2, rt, 12 h, 75%; (e) TBAF, THF, 0 °C, 2 h, 95%.