Tetrahedron 73 (2017) 5220–5228

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel phosphanucleoside analogs of dideoxynucleosides

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ARTICLE INFO

Article history:
Received 27 March 2017
Received in revised form
16 June 2017
Accepted 11 July 2017
Available online 14 July 2017

Keywords:
Phosphanucleoside
Nucleoside analog
Ring-closing metathesis
Stereoselective hydroboration
Chiral resolution

ABSTRACT

The synthesis of modified nucleoside analogs is an attractive area of medicinal research. Here, we have developed a synthetic route leading to a new class of dideoxynucleoside analogs, the phosphanucleosides containing 1-hydroxymethylphospholane 1-oxide rings. The preparation of these compounds consisted of a multistep synthesis of phospholane scaffold using a ring-closing metathesis and stereoselective hydroboration reaction. Subsequent nucleobase construction afforded the phosphanucleosides bearing all four nucleobases. The racemic phosphanucleosides were easily resolved on reverse phase using *N*-acetyl-L-tryptophan as a derivatizing agent.

1. Introduction

Nucleoside analogs have been screened in clinical trials for almost five decades and have become cornerstones for the treatment of various viral infections and cancers. The approval of several new drugs over the past decade demonstrates wide interest in this group of compounds, and demonstrates that these analogs still possess strong therapeutic potentials.[1] Moreover, the rapid evolution of drug resistance has recently become a serious issue. Therefore, the search for novel compounds with antiviral and antimicrobial activities is strongly required.

Sugar-modified nucleosides such as carba-,[2,3] aza-,[4,5] and thia-nucleosides,[6] in which the furanose oxygen is replaced by a carbon, nitrogen, or sulfur atom, respectively, exhibit a variety of interesting biological properties.[7,8] Surprisingly, phosphanucleosides have not received significant attention, and only a few types of these compounds have been reported in the literature.[9–12] Recently, we reported the first comprehensive study on the synthesis of phosphanucleosides bearing all four nucleobases.[13] These compounds resembled the structure of 3-deoxynucleosides.

Encouraged by these results, and intending to extend the scope of phosphanucleoside chemistry, we report here an original set of phosphanucleoside analogs related to dideoxynucleosides. The aimed phosphanucleoside analogs exhibit structural similarity with furanose-based nucleosides, such as 2′,3'-dideoxyinosine (ddI) and 2′,3'-dideoxycytidine (ddC), which were approved as inhibitors of HIV reverse transcriptase.[14] The presence of the 1-oxide group mimicking the 4′-substituent also resembles the structure of anti-HCV compounds.[15,16]

Moreover, we report *N*-acetyl-L-tryptophan as an efficient derivatizing agent for the chiral resolution of racemates of the prepared phosphanucleosides.

2. Results and discussion

Since the publication of our first set of phosphanucleosides,[13] we have significantly improved the synthesis of the key synthon **6** (Scheme 1). The higher yielding and more convenient synthetic route utilized the ring-closing metathesis of diallyl(tritylloxymethyl)phosphine oxide (**10**). In the key step (**10** → **6**), only 1.5 mol% of Grubbs catalyst (1st generation) was used to achieve nearly quantitative cyclization. Compound **10** was easily prepared in three steps starting from diethyl phosphite (**7**) and allylmagnesium bromide followed by the reaction of the diallylphosphine oxide (**8**) with formaldehyde, affording the hydroxymethyl derivative **9**, which was then protected with a trityl group to obtain the desired diallyl derivative **10**.

Hydroboration of phospholene **6** with BH_3*THF complex followed by treatment with aqueous sodium perborate afforded a mixture of *trans* and *cis* racemates **11a** and **11b** in an approximately

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http://dx.doi.org/10.1016/j.tet.2017.07.020
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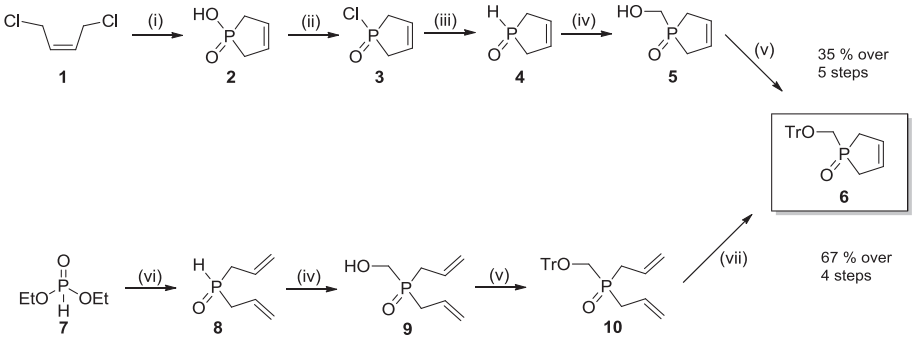


Scheme 1. (i) $NH_4H_2PO_2$, BSA, 110 °C, 72 h; (ii) $(COCl)_2$, DCM, r.t., 16 h; (iii) DIBAL, DCM, −78 °C, 2 h; (iv) CH_2O, TEA, EtOH, r.t., 16 h; (v) Tr-Cl, pyridine, 60 °C, 36 h; (vi) allylMgBr, Et_2O, r.t., 4 h; (vii) Grubb's catalyst, 1st gen., DCM, 50 °C, 6 h.

3:1 ratio (Scheme 2). The major product was identified as the *trans* racemate **11a**. This finding added the phosphine oxide group to the list of already reported functional groups, such as ether, acetate and hydroxy groups,[17–19] which direct stereoselectivity of the hydroboration reaction. In our case, the phosphine oxide group directed *cis* hydroboration. We attempted to improve the stereoselectivity of hydroboration reaction using bulkier borane reagents such as 9-BBN, catecholborane and pinacolborane. Unfortunately, we did not observe formation of the product in any case.

Since we were not able to separate the mixture of hydroxy derivatives **11a** and **11b** on silica gel, we carried out further transformations with the mixture of diastereomers. The hydroxy group was converted to the mesylate using methanesulfonyl chloride in the presence of *N*-methylimidazole in DCM, and subsequently treated with sodium azide in DMF to afford azides **13** and **14**. At this point, azido diastereomers were easily separated using chromatography on silica gel. The substitution reaction was accompanied by approximately 15% elimination. Azides **13** and **14** were hydrogenated at atmospheric pressure in the presence of catalytic Pd/C to provide the corresponding amines **15** and **16** as starting compounds for nucleobase construction (Scheme 3).

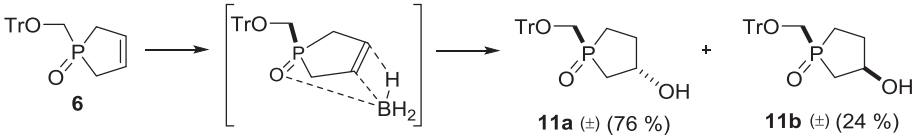
Uracil derivative **19** was prepared from the appropriate amine **15** using 4-nitrophenyl-3-ethoxyacryloylcarbamate **17** (Scheme 4).[20] The reaction of the amine with the nitrophenyl carbamate afforded the ureido derivative **18**, which was subsequently transformed into the uracil derivative *via* acid-catalyzed cyclization.

Adenine (**24**) and guanine (**25**) phosphanucleosides were synthesized using 4,6-dichloro-5-formamidopyrimidine **20** and 2-amino-4,6-dichloro-5-formamidopyrimidine **21**, respectively (Scheme 4).[21] In the first step, the purine rings were formed in a one-pot reaction under heating at 130 °C. The 6-chloropurine derivative **22** was converted into the adenine phosphanucleoside **24** by treatment with aqueous ammonia followed by treatment with acetic acid to remove the trityl group. The 2-amino-6-chloropurine derivative **23** was treated with hydrochloric acid in methanol to afford guanine phosphanucleoside **25**.

Cytosine derivative **27** was prepared from the appropriate DMTr-protected uracil phosphanucleoside, which was treated with 2,4,6-triisopropylbenzenesulfonyl chloride in the presence of triethylamine and *N,N*-dimethylaminopyridine in acetonitrile. TIPS derivative **26** was then converted into the cytosine derivative by treatment with aqueous ammonia. Cleavage of the DMTr group using 80% acetic acid afforded the free cytosine phosphanucleoside **27** (Scheme 4).

Trans dideoxyphosphanucleosides **28**–**31**, resembling α-nucleosides, were prepared using the same protocols as the *cis* derivatives (Scheme 4).

The preparation of dideoxyphosphanucleosides using 1-trityloxymethylphosphol-3-ene 1-oxide (**6**) as a starting precursor afforded the desired compounds in excellent yields. Unfortunately, the phosphanucleosides were afforded as racemic mixtures. To address this issue, we examined several methods to resolve the racemic mixtures on a preparative scale to obtain optically pure enantiomers. As a proof of principle, we chose guanine derivative **25** as a model compound. First, we tried lipase-catalyzed separation of the racemic phosphanucleotide as reported by Garcia et al.[22] Unfortunately, neither the introduction nor the cleavage of the levulinyl group led to the separation of the isomers. Therefore, we derivatized phosphanucleoside **25** with several chiral reagents, such as *R*-mandelic acid, BOC-L-proline, *N*-Ac-L-tryptophan and 1,2:3,4-diisopropylidene-D-galacturonic acid, and examined the chiral resolution on both silica gel and reverse phase. The best results were obtained using 1,2:3,4-diisopropylidene-D-galacturonic acid and *N*-acetyl-L-tryptophan. In both cases, we obtained separation of the enantiomers on reverse phase. Since the ester with galacturonic acid showed lability under the work-up and purification conditions, we selected the tryptophan ester as a chiral resolution group for preparative-scale separation. The Mitsunobu reaction was employed to form the tryptophan phosphanucleoside conjugates (Scheme 5). The diastereomers were easily separated on C18 reverse phase using 0.1% acetic acid in water as a mobile phase, separating the faster-eluting isomer **32** and slower-eluting isomer **33**. Cleavage of the tryptophan ester group of the faster-eluting isomer **32** using aqueous ammonia afforded, after HPLC purification, the pure enantiomer **25(+)** ($[\alpha]_D^{20}$ = + 52.6 (0.156; 20% aqueous methanol)). Similarly, cleavage of the ester group of the slower-eluting isomer **33** afforded the pure enantiomer **25(−)** ($[\alpha]_D^{20}$ = - 52.3 (0.235; 20% aqueous methanol)). The applicability of the tryptophan-based separation protocol on the phosphanucleotides bearing adenine, uracil and cytosine nucleobases is shown in



Scheme 2. Proposed intermediate leading to a diastereoselective hydroboration.