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SYNTHESIS OF NEW CARBOCYCLIC PHOSPHONATE ANALOGS OF DIDEOXYPURINE NUCLEOTIDES

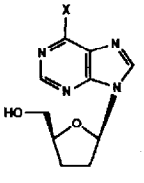
D. Wolff-Kugel and S.Halazy*

Merrell Dow Research Institute Strasbourg Research Center, 16, rue d'Ankara
B.P. 447/R9 67009, Strasbourg , France

Abstract : Three new carbocyclic phosphonate derivatives of adenine **3a**, **3b** and **3c** have been prepared by "purinoselenenylation" from functionalized cyclopentenyl derivatives.

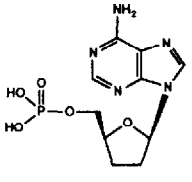
Acquired immunodeficiency syndrome (AIDS) is the result of an infection by the human immunodeficiency virus (HIV)[1]. Certain dideoxynucleoside derivatives have proven to be among the most effective agents to prevent HIV replication[1] as for example 2',3'-dideoxyinosine **1'** (ddI) and 2',3'-dideoxyadenosine **1** (ddA) (scheme 1). Both of these compounds **1** and **1'** are believed to exert their antiviral effect because they are intracellularly transformed into 2',3'-dideoxyadenosine triphosphate (ddATP) which is a potent inhibitor of HIV reverse transcriptase[2]. 2',3'-Dideoxyadenosine monophosphate **2** (scheme 1) has been identified[3] as a common key intermediate in that metabolic processes required for antiviral activity.
These consideration lead us to design new stable synthetic analogs of ddAMP, as potential anti-HIV agents by replacing the oxygen in the sugar ring by a methylene group (in order to avoid the metabolic instability due to the glycosidic bond) and by replacing the labile phosphate monoester of ddAMP by a phosphonate group.

Scheme I

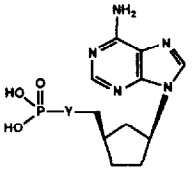


1: ddA (X=NH_2)

1': ddI (X=OH)



2: ddAMP



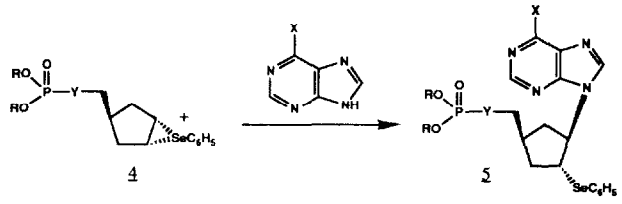
3a: Y =CH_2O

3b: Y= CF_2

3c: Y= CH_2

In this paper, we report the first synthesis of the carbocyclic phosphonates **3a**, **3b** and **3c** as well as a new synthetic method to condense, in one-step, a purine residue with an activated cyclopentyl ring.
Carbocyclic nucleoside analogues are generally[4] better prepared by building up the heterocycle from a functionalized cyclopentylamine derivative. The direct condensation of a nucleic base with an electrophilic cyclopentyl residue is a difficult process as illustrated by the opening of cyclopenten-oxide derivatives with purines[5,6] which gives modest yields of adducts and requires drastic reaction conditions not compatible with phosphonate esters. We disclose herein the opening of a seleniranium salt **4** (scheme II) by a purine derivative. This first illustration of an aminoselenylation[7] including a purine nucleophile is the crucial step for the preparation of the new carbocyclic phosphonate derivatives of adenine **3a-c.**

Scheme II



The unsaturated phosphonate derivatives **7a-c** required to prepare the seleniranium salts **4a-c** have all been obtained from the known[6] 1-hydroxymethyl-3-cyclopentene **6** according to scheme III.

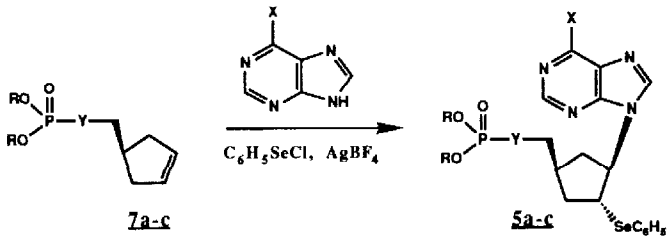
The methoxyphosphonyl derivative **7a** was obtained easily from **6** according to a two steps procedure[8] published for the preparation of acyclic methoxyphosphonyl derivatives of purines. The difluoromethylene phosphonate **7b** was prepared by condensing the triflate obtained from **6** with diethyl difluorolithiomethane-phosphonate[9] and the methylene phosphonate **7c** was obtained by a similar approach using diisopropyl lithio-methane phosphonate.

Scheme III

entry	Y	R	Method	Yield
a	CH_2O	Et	1) HCHO, HCl 2) $P(OEt)_3$, Δ	 61%
b	CF_2	Et	1) $(CF_3SO_2)_2O$, Py 2) $LiCF_2P(O)(OEt)_2$	93% 52%
c	CH_2	iPr	1) TosCl, Et_3N; NaI 2) $LiCH_2P(O)(OEt)_2$	72% 42%

The aminoselenylation of **7a-c** was first studied by using 6-chloropurine as nucleophile (scheme IV). In a typical example, compound **7a** was reacting for 6 hrs with phenylselenenylchloride (1 equiv) in dichloromethane at 20°C ; dichloromethane is eliminated by evaporation and the residue, dissolved in nitromethane, is treated with silver tetrafluoroborate, 6-chloropurine and 1 equivalent of calcium carbonate for 48 hours (Method A).

Scheme IV



7a-c 5a-c

X	Y	R	Method*	Yield(%)
Cl	CH_2O	Et	A	34
Cl	CF_2	Et	A	35
Cl	CH_2	iPr	A	32
Cl	CH_2	iPr	B	46
NH_2	CH_2	iPr	C	15
NH_2	CH_2	iPr	B	46

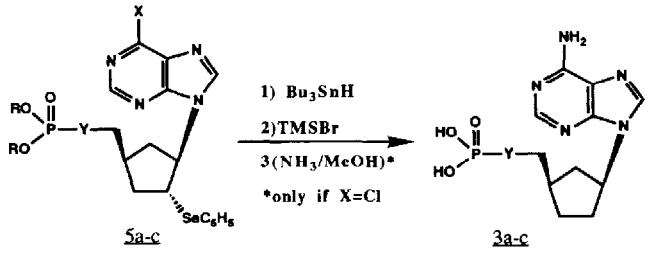
*as described in text

These conditions allowed us to prepare the adducts **5 a-c** (X = Cl) in modest yields but with a good control of the stereoselectivity (> 80%) since the major isomers have been identified by 2D ^1H NMR analysis as those depicted by formula **5**. This stereocontrol is in agreement with the preferential formation of the seleniranium salt **4** which is then stereoselectively opened by 6-chloropurine to give **5**. ^1H and ^{13}C NMR analysis shown only traces of N-7 isomers. When adenine was added with silver tetrafluoroborate to a mixture of **7c** and phenylselenenylchloride in nitromethane (method C), the expected adduct **5c** (X = NH_2) was only obtained in 15 % yield.

Interestingly when these reactions were run in nitromethane under sonochemical activation[11] (scheme IV, method B) yields of the adducts were substantially improved specially when adenine is used as nucleophile. In that latter *case, compound 5c (X = NH_2) was obtained in 46 % yield with 90% stereoselectivity. In that particular case,* 2D 1H NMR NOESY experiments have shown strong interactions between H8 (δ = 7,53 ppm) and $H_{2'}$ (δ = 4,62 ppm) and between $H_{1'}$ and $H_{4'}$ (δ = 2,15 ppm), in agreement with a trans relationship between the selenophenyl and adenine residues and with a cis relationship between the adenine and phosphonoethyl substituants.

The transformation of the intermediate **5c** (X = NH_2) into the target product **3c** was straightforward (scheme V) : the carbon-selenium bond was first cleanly reduced by using tributyltinhydride[12] in the presence of AIBN in toluene at 70°C (78 %) and finally the phosphonate isopropyl protecting groups have been removed by reaction with excess TMSBr[13] in acetonitrile (67 % yield). Compounds **3a** and **3b** have been obtained by the same method from the intermediates **5a** and **5b** (X = Cl) but after subsequent reaction with ammonia in methanol at 100°C in a steel cylinder.

Scheme V



In conclusion, three new carbocyclic analogs of ddAMP have been prepared as potential antiviral agents by using a new purino-selenenylation method which can be improved by sonochemical activation.Work is in progress to apply this new approach to the synthesis of other carbocyclic nucleosides by taking advantage of the versatility of selenium chemistry. Biological data and further details (including the relative yields and structure determination of the stereo- and regio-isomers obtained in scheme IV) will be published in a forthcoming paper.

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