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GLUTARIMIDE NUCLEOSIDES
SYNTHESIS AND PROPERTIES OF ANALOGS OF 1-DEAZA-THYMIDINE

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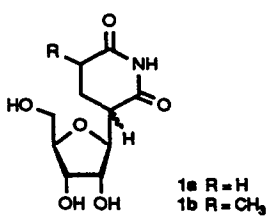
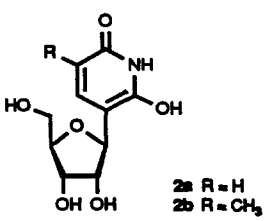
Abstract: *Starting from simple phosphoranes, functionalized glutarimide phosphorus ylids were obtained. Wittig reactions with ribose derivatives produced the corresponding glutarimide nucleosides. Conversion into deaza-thymidine derivatives was unsuccessful, due to the instability of the products.*

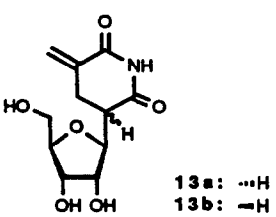
The presence of the glutarimide ring in a variety of natural products and the fact that it has comparable properties with respect to hydrogen bonding to the pyrimidine bases has stimulated us to prepare glutarimide ribosides[1,2]. An additional attractive feature of glutarimide C-nucleosides is the stability of the anomeric bond between base and (deoxy)ribose towards both chemical and enzymatic hydrolysis. So a prolonged existence under biological conditions can be expected, possibly resulting in cytostatic or antiviral agents with improved therapeutic properties.



1a R = H
1b R = CH_3



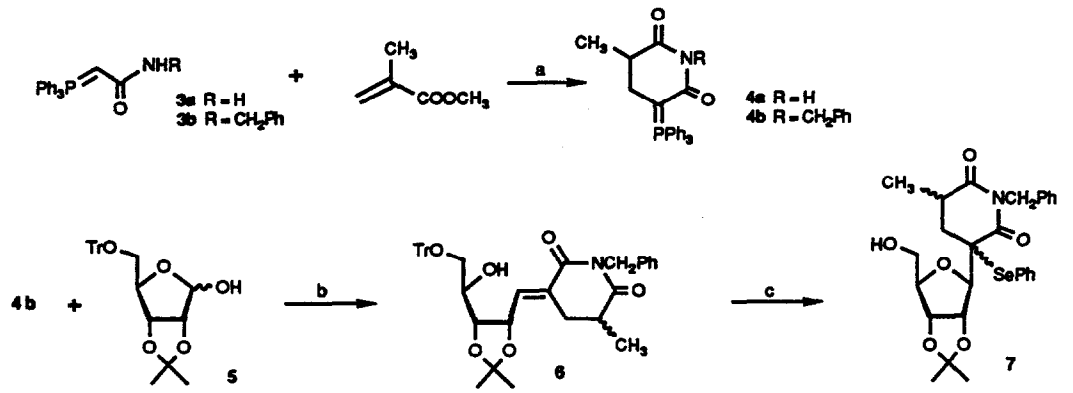
2a R = H
2b R = CH_3



13a: ···H
13b: —H

In a previous publication we described the synthesis of both isomers of the glutarimide ribosides **1a**, as analogs of dihydrouridine[2], via a Wittig reaction followed by base catalyzed cyclization. At that time, on the basis of NMR spectra, we were unable to assign structures to both the diastereomers obtained. Conversion into the 5'- and 3'-anhydronucleosides was unsuccessful, thus obstructing the possibility of nOe studies in rigid systems. Oxidation to the corresponding deaza uridine **2a** failed, due to the known instability of these type of derivatives[3]. From the corresponding deaza-thymidine **2b**, the dehydrogenation product of **1b**, more stability was expected, since the presence of a methyl substituent would disfavour oxidation in this position.

Although the preparation of methyl substituted glutarimide ylide **4a** (see scheme 1) was not successful[2] via a Michael reaction of unsubstituted triphenylphosphoranylideneacetamide **3a** with methyl methacrylate , the precence of a N-benzyl substituent[4] (**3b**) made it possible to obtain ylide **4b** in low yield (22%).



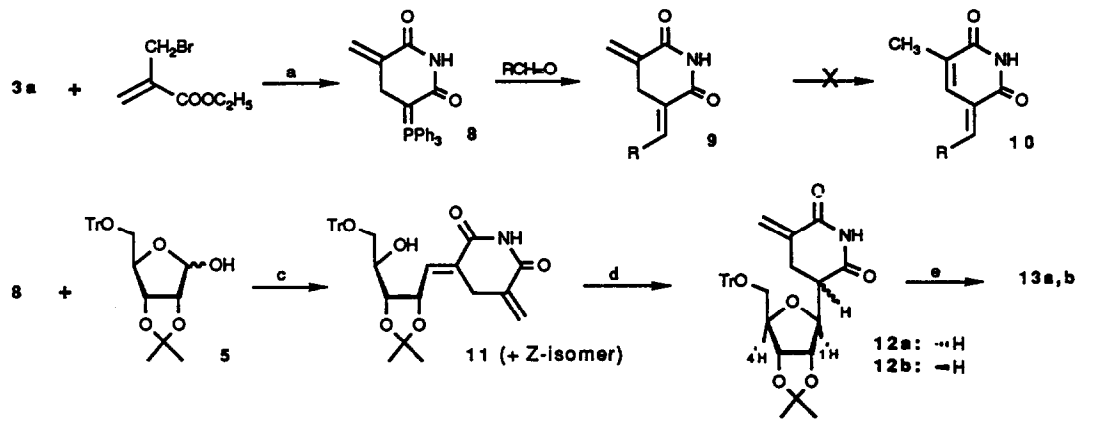
scheme 1

a) CH_3OH, 2.5 eq methyl methacrylate, RT, 16h, then 3h reflux, 22%; b) toluene, reflux, 30h, 53%; c) PhSeCl, CH_3CN, RT, 6h, 41%.

A Wittig reaction of **4b** with 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose **5** in refluxing toluene gave 53% of a mixture of E- and Z-isomers **6** (E:Z = 65:35), each as a mixture of stereoisomers. Ring closure with phenylselenenyl chloride[5,6] yielded an inseparable mixture of glutarimide ribosides **7**, from which the trityl function appeared to be removed by the hydrogen chloride formed during the reaction. Aromatization should destroy both stereocenters in the ring, resulting in the formation of a single compound. Again however, oxidative elimination of the phenylselenenyl substituents from this mixture with for instance H_2O_2, m-CPBA or ozone, did not yield any isolable product. These results may be explained by the phenolic nature of the 2,6-dihydroxypyridine ring, undergoing dimerization and hydroxylation reactions[7] in the presence of phenylseleninic acid[8] (formed by disproportionation or oxidation of PhSeOH).

To accomplish aromatization in the absence of oxidants, our attention was directed towards the unsaturated glurarimide nucleosides **13a,b**, from which deaza-thymidine **2b** could in principle be obtained by acid or base catalyzed double bond isomerization. Phosphorane **3a** (obtained from chloro acetamide and triphenyl phosphine[9]) reacted smoothly with ethyl bromomethacrylate. The unsaturated glutarimide phosphorane **8** is a reasonably stable solid, capable of reacting with several aliphatic and aromatic aldehydes, leading to unsaturated glutarimides of general structure **9** (table 1). Isomerization of one of the double bonds of the unsubstituted product (**9**, R=H) into the endocyclic conjugated system (**10**, R=H) failed under many different conditions.

Condensation of **8** with 2,3-O-isopropylidene-5-O-trityl-D-ribofuranose (**5**) produced **11** in 46% yield (E:Z = 62:38) An explanation for the relative high amount of Z-isomers from Wittig reactions with some ribose derivatives has recently been given[10]. Cyclization occurred upon treatment with diazabicycloundecene to give **12** as a 40:60 mixture of isomers, which could be separated by flash chromatography. Both isomers of 1-deaza-thymidine **13a** and **13b** were obtained by deprotection with trifluoroacetic acid. Again isomerization of the exocyclic double bond into the glutarimide ring failed.



scheme 2

a) powdered K_2CO_3, CH_3OH, 0°, 4h, 82%; b) see Table; c) $CHCl_3$, reflux, 64h, 46%;
d) DBU, CH_2Cl_2, 0°, 15 min, 89%; e) THF/H_2O/TFA 10:5:1, reflux, 90 min, 96% (**12a**) and 95% (**12b**).

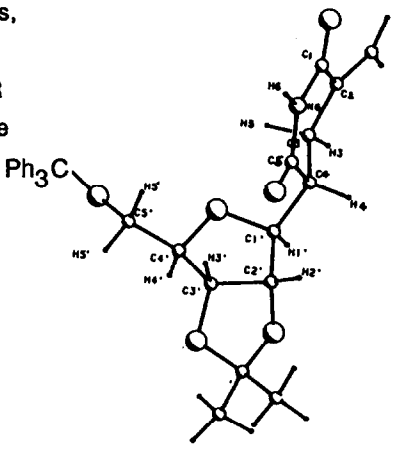
Table 1: **Wittig reactions with 8**

	product	solvent	conditions	yield	E/Z
9a:	R = H	DCE	reflux, 40 min,	79%	_
9b:	R = p-NO_2Ph	CH_2Cl_2	RT, 4h,	90%	E
9c:	R = Ph	DCE	reflux, 5h,	82%	E
11:	R = ribose	$CHCl_3$	reflux, 64h,	46%	E:Z = 62:38

Via nOe-difference spectroscopy, in both **12a** and **12b** the beta anomeric configuration could be established, the proximity of H-1' and H-4' being clearly visible. Since one of the protected derivatives was obtained in a crystalline form, an X-ray analysis[11] was used to assign the orientation

of the proton at C-4 (glutarimide numbering). From this, it could be unequivocally established, that the crystals were obtained from isomer **12b**. Comparison of the NMR spectra finally also allowed structural assignments to the isomers of **1a**.

The exocyclic double bond, as expected, exhibited strong electrophilic properties. Reaction of several derivatives of **9** with thiols and cystein, and cytostatic properties found, will be published elswhere.



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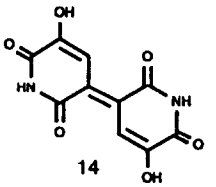

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