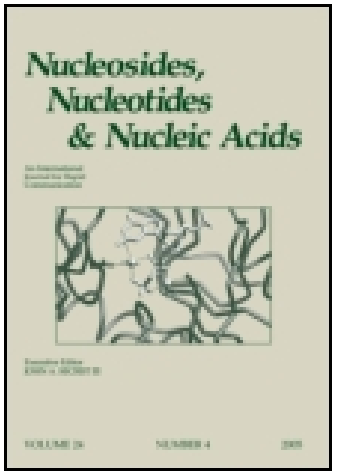

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A Versatile Synthesis of Enantiomerically Pure D- and L-Pyranosyl Nucleoside Analogues

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A VERSATILE SYNTHESIS OF ENANTIOMERICALLY PURE D- AND L-PYRANOSYL NUCLEOSIDE ANALOGUES

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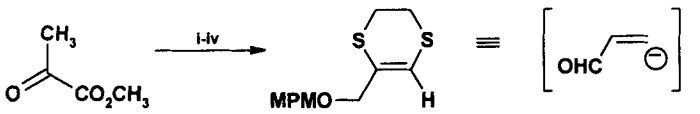
ABSTRACT: 2-[[*O*-(*p*-Methoxybenzyl)-oxy]methyl]-5,6-dihydro-1,4-dithiin **1** is a versatile three carbon homologation reagent which has been conveniently used in the synthesis of enantiomerically pure modified nucleosides.

Nucleoside analogues with a six-membered modified carbohydrate moiety have been used as building blocks of synthetic oligonucleotides, due to their known *in vitro* antiviral activity[1]. Therefore, the synthetic methodologies to obtain these molecules have received a great impulse during the last decade. As a part of our current interest in the carbohydrate chemistry we report now a new versatile synthesis of D- and L-nucleosides bearing a six-membered acetal ring.

Scheme 1



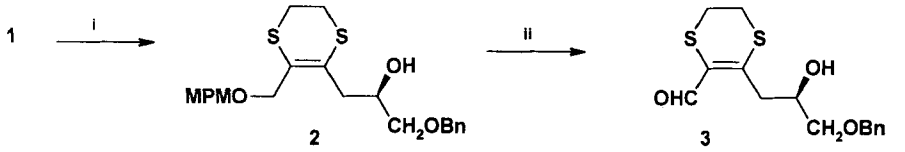
1

i: Polymer bound PPh_3/I_2/ethanedithiol in CH_2Cl_2; ii: NBS in $CHCl_3$; iii: $LiAlH_4$ in THF; iv: NaH in DMF, then *p*-methoxybenzyl chloride

The key step of the procedure is represented by the homologation of either (*S*)- or (*R*)-benzyl glycidyl ether by 2-[[*O*-(*p*-methoxybenzyl)-oxy]methyl]-5,6-dihydro-1,4-dithiin **1** which acts, in fact, as a masked acyl β-anion equivalent[2].

The compound **1** was readily prepared from pyruvate in high overall yield (83%), as is shown in Scheme 1. After treatment with BuLi, **1** was coupled with commercial (*R*)-benzyl glycidyl ether to give **2**. It is noteworthy that the cleavage of the MPM protecting group, by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2/H_2O, afforded a carbaldehyde function instead of a primary hydroxyl group[3] (Scheme 2), likely due to the presence of the β sulfur atom and the consequent extra stabilization of the allylic carbocation[2] resulting from the initial electron transfer fission step.

Scheme 2

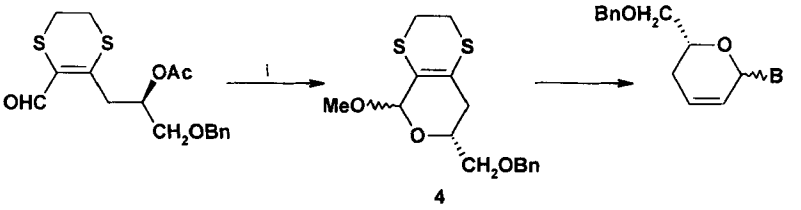


i: BuLi in THF, then (*R*)-benzyl glycidyl ether, -78 °C; ii: DDQ in CH_2Cl_2/H_2O.

The carbaldehyde bearing product **3** acetylated, when treated with TMSOTf and NEt_3 in MeOH, straight underwent the closure of the six-membered acetal ring, leading to **4**.

Sulfur removal[4] from **4**, followed by standard coupling[5] with silylated bases, eventually afforded the modified L-nucleosides, as show in Scheme 3.

Scheme 3



i: TMSOTf, NEt_3, MeOH.

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