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Stereoselective synthesis of L-isonucleosides

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Abstract—L-Isonucleosides **17** and **19** were stereoselectively synthesised from (*S*)-glycidol by two different procedures. The key step was the synthesis of a chiral dihydrofuran which was carried out by oxidation/elimination of **8** and by ring-closing metathesis of diene **10**. The procedure can be applied to the synthesis of both enantiomers.

Although most new nucleoside analogues reported are D-nucleosides, during the last decade L-nucleosides have emerged as a new class of biologically active compounds.[1] Isonucleosides[2] are also promising therapeutic agents, since some of them combine strong and selective anti-HIV and anti-HSV activity with higher stability towards acid and enzymatic degradation. For example, the (*S*,*S*)-isomer of the deoxy-isonucleoside *iso*-ddA[3] (Fig. 1) has an anti-HIV activity similar to that of ddA, and no apparent toxicity. Interestingly, its enantiomer [(*R*,*R*)-isomer] has a similar range of activity. We have recently published a synthesis of (*S*,*S*)-*iso*-ddA from glycidol which allows both enantiomers to be prepared by choosing the configuration of the starting material.[4]

D-Isonucleosides (**1**, Fig. 1) were first prepared by Montgomery,[5] and later Nair[6] carried out an intensive study of these isonucleosides, including the synthesis of oligonucleotides.[7] However, there are few reports describing the synthesis of L-isonucleosides (**2**).[8]

Isonucleosides are synthesised by reacting an activated 1,4-anhydroalditol derivative with the purinic or pyrimidinic base. The 1,4-anhydroalditol moieties are usually prepared from carbohydrates (Scheme 1).[5–9] D-Ribose is the starting material for synthesising D-hydroxyderivatives such as **1**, through deoxygenation of the anomeric position to give derivative **3**. L-Isonucleosides are prepared from 3,5-di-*O*-mesyl-D-xylose, via a rearrangement to give L-sugar **4**.[8] This is followed by formation of the epoxide **5**, which is opened by a nucleic base. Only a few reports describe the asymmetric synthesis of 1,4-anhydroalditol units.[10]

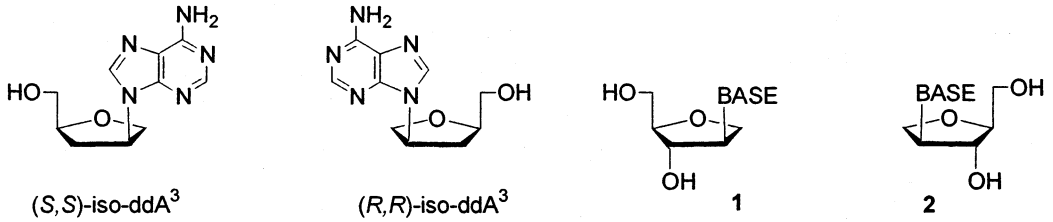

Figure 1.

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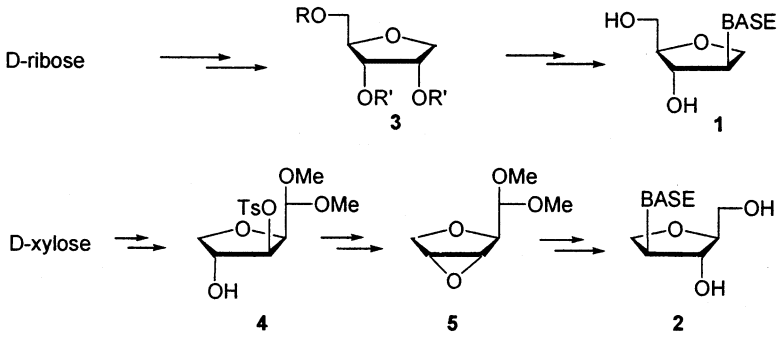
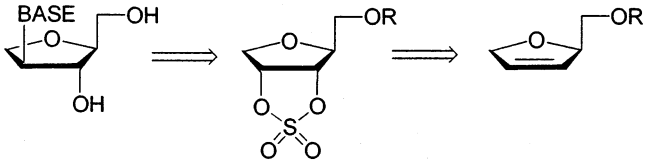


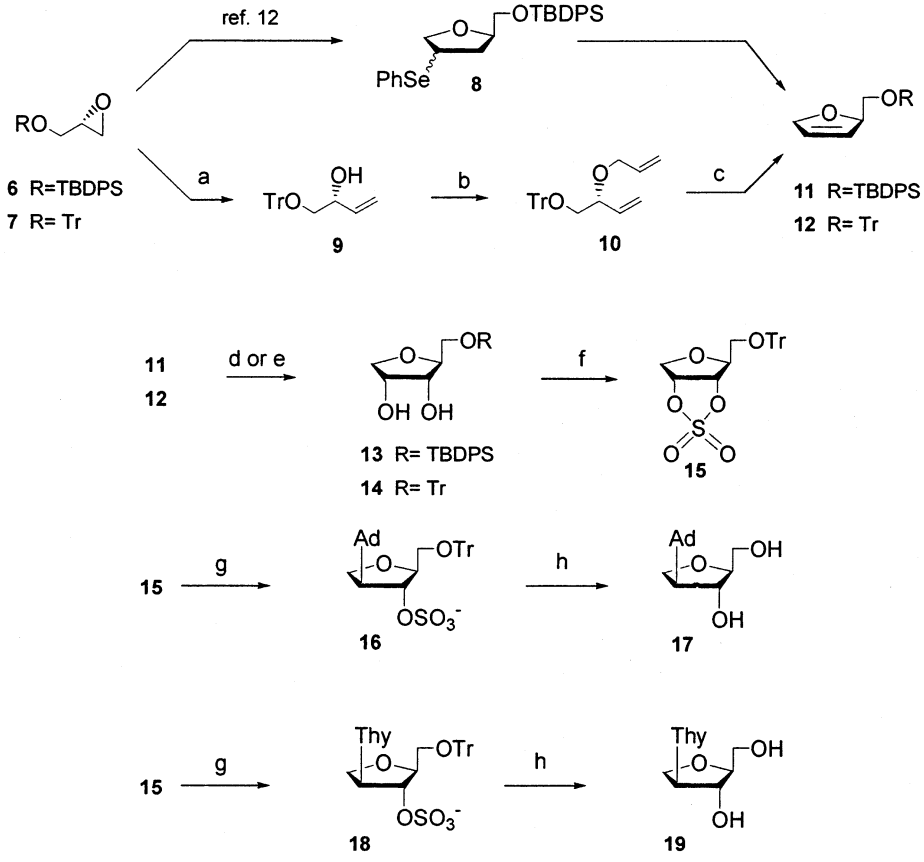
Scheme 1.



Scheme 2.

Continuing with our interest in developing procedures for the synthesis of both D- and L-isonucleosides, we report in this paper the stereoselective synthesis of L-isonucleosides (**2**) from (*S*)-glycidol.

Recently, Nair reported an efficient procedure for introducing nucleic bases by opening a cyclic sulfate.[11] Bearing this in mind, we decided to obtain the



Scheme 3. *Reagents and conditions*: (a) $(CH_3)_3SI$, BuLi, THF, 0°C, 2 h, 69%. (b) 1. NaH, THF, from −18°C to reflux, 2 h, 2. $BrCH_2CH{=}CH_2$, rt, 2 h, 92%. (c) Grubbs catalyst, CH_2Cl_2, rt, 4 h, 78%. (d) $K_2OsO_4{\cdot}2H_2O$, NMO, ^{t}BuOH/DMF, rt: **13**, 36 h, 91%, *cis*:*trans* = 1:9; **14**, 3.5 h, 78%, *cis*:*trans* = 1:4. (e) $RuCl_3$, $NaIO_4$, CH_3CN/AcOEt/H_2O, −20°C: **13**, 3 h, 35%, only *trans*; **14**, 2 h, 70%, *cis*:*trans* = 1:10. (f) 1. Cl_2SO, py, rt, 12 h, 90%, 2. $RuCl_3$, $NaIO_4$, CCl_4/CH_3CN/H_2O, 0°C, 2 h, 88%. (g) Adenine or thymine, DBU, CH_3CN, reflux, 2.5 h, then **15**, 2.5 h. (h) 3% HCl in MeOH, reflux, 24 h: **17**, 67% (two steps); **19**, 62% (two steps).

precursor diol by dihydroxylation of the corresponding dihydrofuran (Scheme 2).

We recently described the synthesis of the enantiopure dihydrofuran **11** by regioselective elimination of the selenoxide derived from **8**, which in turn had been obtained in a straightforward manner from glycidol **6** (Scheme 3).[12] Some reports describe that stereoselectivity in the hydroxylation of related compounds depends on the solvent[13] and the substituents in the substrate.[14] We explored different reaction conditions for the hydroxylation of dihydrofuran **11**. Treatment with K_2OsO_4/MNO in ^{t}BuOH–DMF gave 1,4-anhydroalditol **13** in 91% yield (*cis*:*trans* = 1:9). Dihydroxylation with $RuCl_3/NaIO_4$, albeit much faster and selective (only the *trans* isomer was isolated) gave a smaller yield of **13** (35%). This compound is the enantiomer of the intermediate prepared by Nair in the reported synthesis of isonucleoside **1**.[11]

On the other hand, in recent years the metathesis reaction[15] has emerged as an efficient synthetic methodology for preparing unsaturated cycles of medium and large size, and we decided to use it to prepare the dihydrofuran intermediate.

Thus, we started from glycidol **7** and chose the trityl protecting group in order to deprotect it during the acid treatment subsequent to the sulfate opening. Treatment of **7** with the sulfur ylide $CH_2{=}SMe_2$ gave the butenediol **9** in 69% yield.[16] Subsequent allylation of **9** with allyl bromide in basic medium afforded the diene **10** in excellent yield. The diene **10** was then submitted to a RCM process by reaction with $RuCl_2(CHC_6H_5)$-$[P(C_6H_{11})_3]_2$ to give dihydrofuran **12** in 78% yield.[17,18] Then we treated **12** with $K_2OsO_4{\cdot}2H_2O$/NMO to obtain the 1,4-anhydroalditol **14** in 78% yield in a *cis*:*trans* ratio of 1:4. In this case, the dihydroxylation with the $RuCl_3/NaIO_4$ system furnished **14** in 70% yield (*cis*:*trans* = 1:10).

Sulfate **15** was obtained by treating **14** with thionyl chloride and further oxidation with $RuCl_3$–$NaIO_4$.[11] The bases were introduced following the procedure described by Nair to give the compounds **16** and **18**, which were directly submitted to acid treatment to provide the isonucleosides **17** and **19** in 67 and 62% yield, respectively.

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