Towards chiral 1,2-propanediols via desymmetrization

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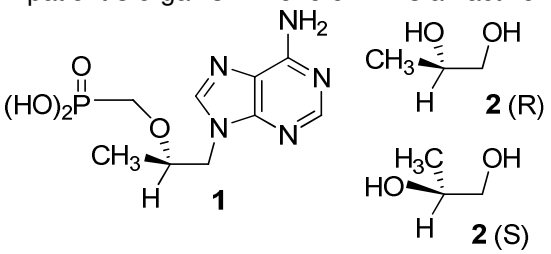
INTRODUCTION

General tendency in the pharmaceutical industry is to use either a chiral substrates or to perform chiral separations to obtain only one specific isomer as an active principle in order to decrease a metabolic load in patient´s organism. Tenofovir **1** is an active

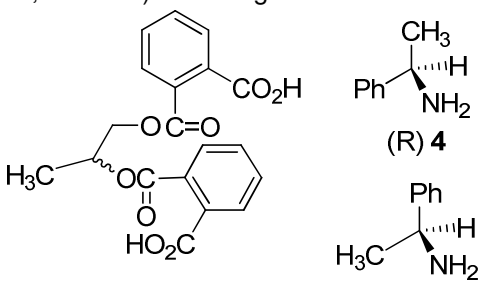


1 **2** (R) **2** (S)

principle of the Viraed® and is liberated from its pro-drug form. Viraed® is approved for treatment of HIV and HBV infections as an inhibitor of reversed transcriptase. One of the components of Tenofovir is (R)- 1,2-propanediol **2**. Reported here are initial stages of obtention of (R) **2** and its enantiomer (S) **2** *via* desymmetrization of easily available glycerol and racemic 1,2-propanediol.

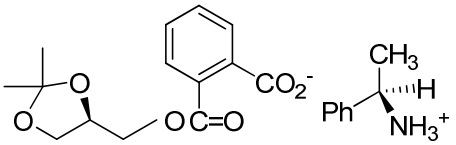
RESULTS AND DISCUSSION

Our initial attempts to use biphthalate **3** and derivatives of aminoacids as chiral auxiliaries (L-lysine, L-serine) were negative. Inconsistent results

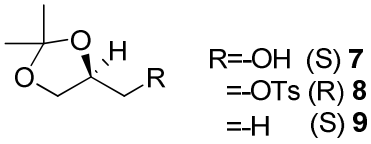


3 (R) **4** (S) **5**

were obtained during application of brucine: even though a crystalline material was obtained which was submitted for x-ray analysis, the process of crystallization was difficult to reproduce, and this approach was abandoned, even though application of strychnine was published for the same purpose.[1] Since both (R) and (S)-1-phenylethylamines **4** and **5**, respectively, are available commercially, we used them next. Disappointingly, a salt formed between **3** and **4** is not a crystalline material. However, a phthalate **6** derived from racemic 1,2-isopropylideneglycerol and amine (R) **4**[2,3] permitted to obtain (S) 1,2-isopropylidene glycerol **7** *via* a series of crystallizations, followed by removal of



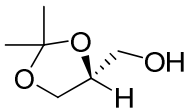
6 (R)



R=-OH (S) **7**
=-OTs (R) **8**
=-H (S) **9**

chiral auxiliary and phthalate moiety. Tosylate (R) **8** derived from (S) **7** is a precursor of (S) **9**, which in turn permits obtention of the target (S) **2** (*via* $NaBH_4$ reduction and hydrolysis).

Following the same procedure, racemic phthalate **6** on treatment with the amine (S)-**5** furnished a salt which is a precursor of (R) **10** and eventually of the (R) **2**.



(R) **10**

Work is underway to find a method to obtain both enantiomeric diols **2** directly from racemic **3** in order to avoid tosylation and reduction.

CONCLUSION

Desymmetrization of phthalate **6** using auxiliary amines **4** and **5**, followed by simple reduction is a way to access both diols (R) and (S) **2**.

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