Synthesis of enantiomerically pure antimalarial carbocyclic nucleoside phosphonates

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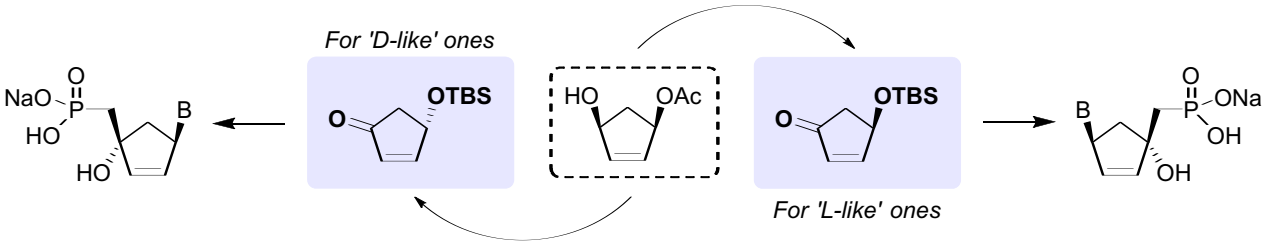
Plasmodium falciparum (*Pf*) is a protozoan parasite responsible for the most lethal form of malaria, which is a major health threat in tropical and subtropical countries. In 2024, the World Health Organization (WHO) estimated that malaria is the root of 610,000 deaths and 282 million cases worldwide, the latter having increased for the sixth consecutive year.[1]

Carbocyclic nucleosides (or carbonucleosides) are analogs of the natural nucleosides in which the furanose oxygen of the latter compounds has been replaced by a methylene group. Our recent results highlighted the potency of purine containing carbonucleoside phosphonates as antimalarial compounds, with a notable difference between 'D-like' and 'L-like' enantiomers.[2]

Synthetically, these molecules can be obtained from a 4-*tert*-butyldimethylsiloxy-2-cyclopentenone as starting material.[2] Literature provides different examples to prepare the two enantiomeric forms from the commercially available (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate[3–5], but the synthesis of (4*R*)-(+)-*tert*-butyldimethylsiloxy-2-cyclopentenone either requires the use of enzymes[6] or a significant number of steps.[7] Additionally, the enantiomeric excess appreciation is only based on an unsatisfying optical rotation measure.

Therefore, we developed an efficient and scalable synthetic procedure to obtain both 4-*tert*-butyldimethylsiloxy-2-cyclopentenone enantiomers (Scheme) while validating their enantiomeric purity by chiral chromatography analysis. These two building blocks were then incorporated in our developed methodology[2,8] to give rise to the enantiomerically pure 'D-like' and 'L-like' carbocyclic nucleosides.



Scheme: Our strategy towards the synthesis of enantiomerically pure 'D-like' and 'L-like' carbonucleosides from commercially available (1*R*,4*S*)-(+)-4-hydroxy-2-cyclopentenyl acetate.

References

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