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Asymmetric synthesis of unsaturated α-benzyloxyaldehydes: an enantioselective synthesis of (+)-*exo*-brevicomin

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Abstract—Enantioselective synthesis of α-hydroxy aldehydes with an alkene tether was accomplished from L-(+)-tartaric acid, employing stereoselective reduction of a 1,4-diketone with L-selectride as the key step. Synthetic utility of these aldehydes was demonstrated in the synthesis of pine beetle pheromone (+)-*exo*-brevicomin.

1. Introduction

The synthesis of bio-active natural products with the aid of building blocks derived from chiral pool sources is an attractive method in organic synthesis.[1] In this context, naturally occurring α-hydroxy carbonyl compounds have been explored extensively in natural product synthesis.[2] However, their higher homologues bearing a longer carbon chain with or without further functionalities are scarce from chiral pools. These types of carbonyl compound serve as excellent building blocks for the synthesis of chiral 1,2-difunctional compounds, for example, 1,2-amino alcohols and 1,2-diols, which have numerous applications in the enantioselective synthesis of natural products. We were interested in the synthesis of α-hydroxy aldehydes/acids having an alkene tether, which could be further applied to the synthesis of a number of oxygen-containing heterocycles. Although there are a few examples of the synthesis[3] of such types of compounds, a general approach is essential. Herein, we report a general method for the synthesis of α-hydroxy aldehydes having an alkene tether starting from chiral pool tartaric acid. The further synthetic utility of these aldehydes is demonstrated by application to the synthesis of the pine beetle pheromone (+)-*exo*-brevicomin.

2. Results and discussion

Recently, we reported the synthesis of α-methoxyarylacetic acid derivatives from L-(+)-tartaric acid, involving a very highly diastereoselective reduction of a C_2-symmetric 1,4-diaryl diketone with K-selectride[4] (Scheme 1).

Encouraged by this strategy, we anticipated that reduction of the C_2-symmetric 1,4-alkenyl diketones **2**, should furnish the C_2-symmetric 1,4-diols **3**, precursors for the title compounds. Thus, diketones **2a** and **2b** were prepared by the addition of the respective Grignard reagents to bis-Weinreb amide[5] **1** of tartaric acid. Subsequent reduction of diketone with L-selectride resulted in a single diastereomer of diols **3a** and **3b** in very high yields. The formation of the other possible two diastereomers (C_1-symmetric diastereomer and the other C_2-symmetric diastereomer) was not observed within detectable limits by ^{1}H NMR (Scheme 2).

Protection of the diols as benzyl ethers **4a**–**b** was effected with sodium hydride and benzyl bromide in almost quantitative yield. Facile deprotection of the acetonide of the benzyl ethers was executed with ferric chloride[6] to furnish the corresponding 1,2-diols **5a** and **5b** 94% and 89% yield, respectively, which upon treatment with lead tetra acetate in benzene resulted in the quantitative formation (2 mol) of aldehydes **6a** and **6b** (Scheme 3). Stereochemical integrity was preserved all through the transformations. The configuration at the newly formed stereogenic center was further established by comparing specific rotation of alcohols **7a** and **b** {$[\alpha]_D$ for

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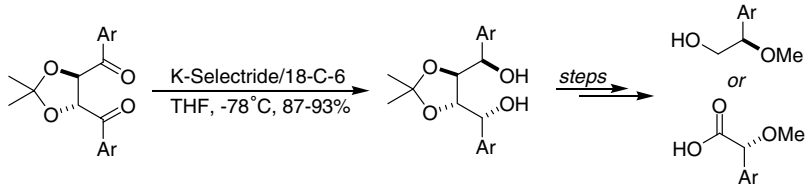
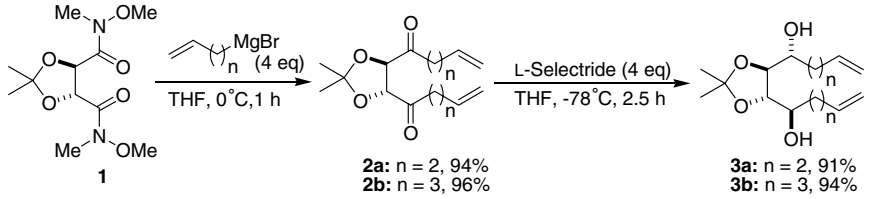
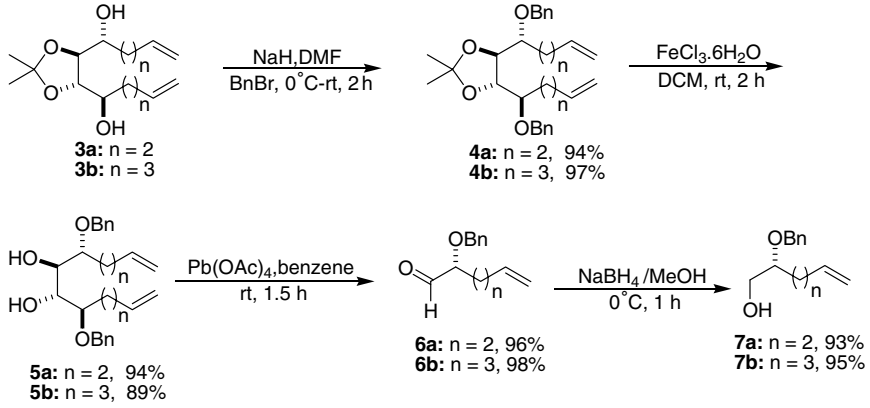


Scheme 1. Asymmetric synthesis of α-methoxyarylacetic acid derivatives.



Scheme 2. Stereoselective reduction of 1,4-diketones derived from L-(+)-tartaric acid.

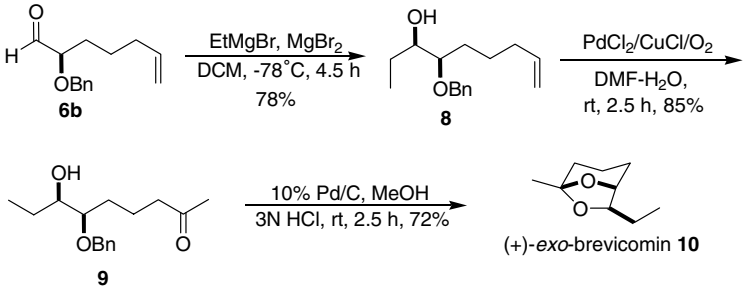


Scheme 3. Synthesis of enantiopure α-benzyloxyaldehydes.

7b = −11.8 (*c* 1.9 $CHCl_3$), lit.[3e] −12.2 (*c* 1.8 $CHCl_3$)} obtained from the reduction of aldehydes **6a** and **6b**.

The synthetic potential of these hydroxy aldehydes **6a** and **6b** is widespread, and they serve as excellent precursors for a number bio-active oxygen containing compounds. To demonstrate the utility of these chiral aldehydes, the synthesis of pine beetle pheromone (+)-*exo*-brevicomin[7] was undertaken.

The pheromone *exo*-brevicomin **10** is an aggregation pheromone produced by *Dendroctonus brevicomis*, the western pine beetle, which is a principle pest in the timber regions of the west coast of North America. The synthesis of (+)-*exo*-brevicomin is outlined in Scheme 4. Aldehyde **6b** was treated with ethylmagnesium bromide in the presence of magnesium bromide in dichloromethane to yield the corresponding *threo* alcohol **8** as a single diastereomer in 78% yield.[8] Wacker oxidation[9] of alcohol **8** with $PdCl_2$/CuCl produced ketone **9** (85% yield, $[\alpha]_D$ = −12.8 (*c* 1.3, $CHCl_3$), lit.[10] +13.0 (*c* 1.7, $CHCl_3$) for the corresponding enantiomer). Simultaneous debenzylation and intramolecular acetalization with Pd/C in MeOH and a trace of 3 M HCl transformed **9**



Scheme 4. Synthesis of (+)-*exo*-brevicomin.

into (+)-*exo*-brevicomin {$[\alpha]_D = +66.6$ (*c* 0.3, Et_2O), lit.[8] $= +66.7$; (*c* 1.40 Et_2O)} in 72% yield.

3. Conclusion

In summary, a high yielding approach for the synthesis of α-hydroxy aldehydes tethered to an alkene was accomplished by stereoselective reduction of a 1,4-diketone derived from tartaric acid. The synthetic utility of this methodology was illustrated by applying it to the enantioselective synthesis of (+)-*exo*-brevicomin. Synthesis of further functionalized hydroxy aldehdyes/acids and their potential use as building blocks in oxygen containing heterocycles is in progress.

Acknowledgements

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