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Enantiospecific synthesis of (−)-muricatacin from L-(+)-tartaric acid

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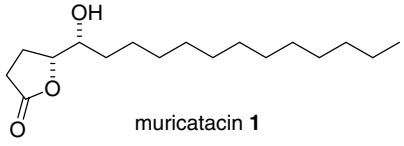
Abstract—Enantiospecific synthesis of (−)-muricatacin, a bio-active lactone comprising of a 5-hydroxyalkylbutan-4-olide structural component has been achieved from L-(+)-tartaric acid. The key step involves a disteroselective reduction of a C_2-symmetric 1,4-diketone derived from tartaric acid followed by a selective Grignard reagent addition.

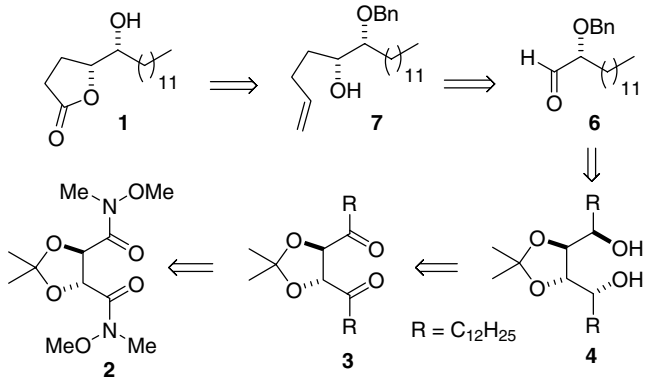
1. Introduction

Annonaceae acetogenins from the Annonaeceae plants have attracted considerable interest owing to their potential biological properties including cytotoxic, antitumoral and immunosuppressive activities.[1] One of the common structural components of these increasingly significant natural products is the chiral 5-hydroxyalkylbutan-4-olide nucleus. Some of the compounds possessing this structural moiety have been shown to exhibit varied biological activities and also shown to be precursors for the synthesis of complex natural products.[2] One of the simple molecules belonging to this group is muricatacin **1**, isolated as a mixture of enantiomers from the seeds of *Anona muricata* L., commonly known as sour soup or guanabana which is grown commercially as a fruit crop in tropical regions.[3] The enantiomers of muricatacin exhibited potent cytotoxicity towards several human tumor cell lines. SAR studies indicated that the activity is influenced by the nature of the side chain,[4] although, diastereomers of muricatacin showed no significant affect on the cytotoxicity.[5] Several syntheses of muricatacin and its congeners have been developed in recent years due to the chemical and biological properties of the molecule.[6] However, a general methodology for the synthesis of functionalized and non-functionalized muricatacin derivatives is still warranted. Herein, we report such a methodology for the synthesis of muricatacin, which is amenable for access to diverse structural derivatives.



2. Results and discussion

Our approach for the synthesis of muricatacin is based on the strategy we developed for the enantioselective synthesis of α-hydroxy aldehydes. We have recently shown that a series of α-hydroxy aldehydes can be obtained in high enantiomeric purity from L-(+)-tartaric acid involving simple stereoselective transformations.[7] As depicted in retrosynthesis (Scheme 1), we anticipated the synthesis of



Scheme 1. Retrosynthesis for (−)-muricatacin.

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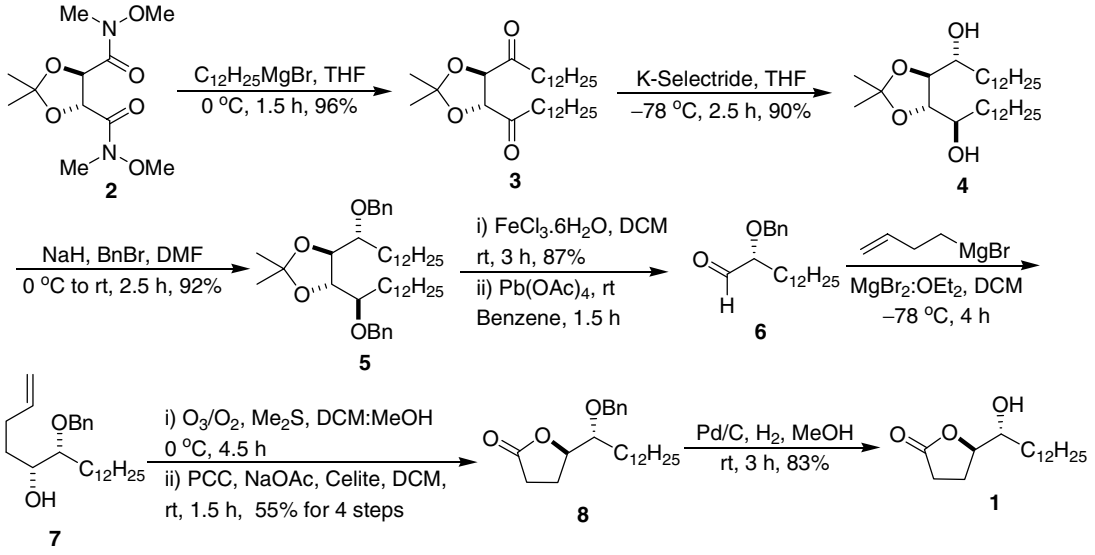

Scheme 2. Stereoselective synthesis of (−)-muricatacin.

muricatacin by elaboration of alcohol **7**, which can be obtained by a stereocontrolled Grignard addition to aldehyde **6**. Aldehyde **6** can be accessed from diol **4**, which in turn can be achieved by the stereoselective reduction of the diketone **3**. Diketone **3** was derived by the addition of dodecylmagnesium bromide to the bis-Weinreb amide **2** of tartaric acid.

Our synthetic sequence started with the addition of dodecylmagnesium bromide to the bis-Weinreb amide **2**[8] to afford diketone **3** in excellent yield. Under conditions optimized by us previously for the reduction of such diketones,[7] the reduction of 1,4-diketone **3** with K-Selectride produced alcohol **4** as a single diastereomer. Protection of the alcohol as the corresponding benzylether was effected utilizing NaH/BnBr to yield dibenzylether **5** in 92% yield. Deprotection of the acetal in **5** furnished the corresponding diol, which upon treatment with $Pb(OAc)_4$ afforded aldehyde **6**, which was used as such in the next step.[9] Reaction of aldehyde **6** with 3-butenylmagnesium bromide in the presence of $MgBr_2{\cdot}Et_2O$ in dichloromethane provided alcohol **7**.[10] High selectivity associated with the formation of alcohol **7** can be explained based on the chelation controlled addition of the Grignard reagent to the aldehyde. Ozonolysis of alcohol **7** yielded the corresponding lactol, which on oxidation with PCC afforded lactone **8** in 55% yield in four steps. Debenzylation of lactone **8** with Pd/C proceeded cleanly to afford muricatacin **1**. A synthetic sample of (−)-muricatacin **1** {mp 67–67.5 °C, $[\alpha]_D = -23.6$ (*c* 1.1, $CHCl_3$) lit.[11] mp 67–68 °C, $[\alpha]_D = -23.3$ (*c* 1.8, $CHCl_3$)} exhibited spectral data identical to those reported in the literature (Scheme 2).

3. Conclusion

In conclusion, a concise and enantiospecific synthesis of bio-active lactone, (−)-muricatacin was achieved from L-(+)-tartaric acid. The synthetic sequence presented is simple, highly diastereoselective, and is amenable for the synthesis of a number of functionalized and non-functionalized derivatives of muricatacin. Further application of this strategy for the synthesis of a number of bio-active lactones is in progress.

Acknowledgements

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9. Enantiomeric excess of the aldehyde **6** was determined by the following. $NaBH_4$ reduction of aldehyde **6** afforded the corresponding primary alcohol, which was derivatized to the diastereomeric carbonate with (−)-menthyl chloroformate. ^1H NMR spectra of the carbonate revealed the de as >95% with in detectable limits.
10. Alcohol **7** was produced in 74% yield contaminated with a small amount of an unidentified compound. However, this does not hamper the outcome and purity of the products in the subsequent reaction sequence. A similar outcome in the addition of vinylmagnesium bromide in dichloromethane as solvent to aldehyde **7** is known in the literature (Ref. 6g).
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