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Synthetic Studies of Didemnaketals Analogue-Construction of the Intermediate (3S,5S,6R)-3,7-Dimethyl-5,6,7-trihydroxy-octanal

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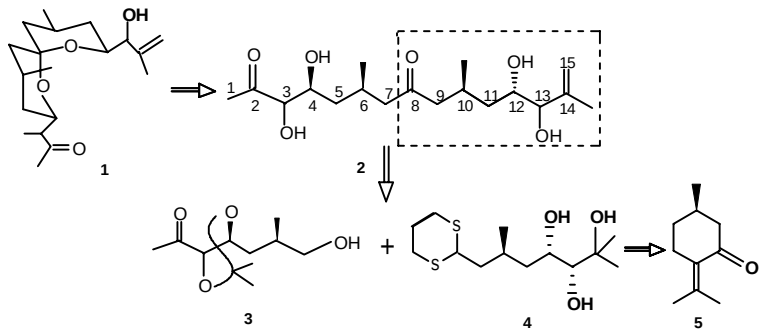
Abstract: An efficient and stereoselective synthetic procedure for (3S,5S,6R)-3,7-dimethyl-5,6,7-trihydroxy-octanal derivative, the intermediate for synthetic of the HIV-active didemnaketals analogue, was developed *via* a series of reactions from the natural (+)-Pulegone. In this approach, an efficient diastereoselective reaction of the epoxides **8** and **9** with PCC has been accomplished.

Keywords: Didemnaketals, stereoselective synthesis, diastereoselective reaction.

The Didemnaketals A and B have been reported to be significant inhibitors to HIV-protease[1]. In connection with the total synthesis of this kind of compounds, our recent research interest is focused on their synthetic studies as well as synthesis of an analogue **1**, which incorporated the key spiroketal moiety of the didemnaketals A and B. Based on the retrosynthetic consideration(**Scheme 1**), the linear intermediate **2** would be constructed from **3** and **4**. Furthermore, **4** would be synthesized from (+)-Pulegone **5**. We herein reported a stereoselective synthetic procedure for the (3S,5S,6R)-3,7-dimethyl-5,6,7-trihydroxy-octanal derivative **4**.

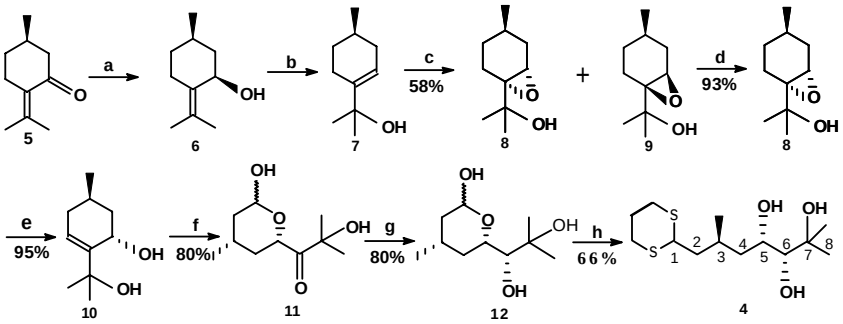
Scheme 1



In our earlier primary investigation[2], (+)-pulegone **5** was converted into **11**. But in fact, the epoxides **8/9**(75:25) were hard to separate by chromatography and the following rearrangement products from mixed **8/9** were very complicated. Here, we have made a

great attempt to separate **8** and **9**, finally we found **9** was consumed during reaction with PCC and **8** was recovered in 93% yield and thus hemi-acetal **11** (2 isomers, 1:1) was obtained more efficiently. We thought this selective oxidation possibly involved an opposite attacking of PCC at the epoxy, and therefore the steric hindrance of the C4-Me of **8** kept it from reaction. In subsequent investigation, the neighboring diastereoselective semi-acetal ring was used to induce the reduction of C_6-carbonyl, and the reduction of the mixed **11** with $NaBH_4$ at –78°C gave the diastereoseletively pure product **12** (2 isomers, 1:1) in 80% yield. Compound **12** was successively protected with 1,3-propanedithiol to give the compound **4** in a yield of 66%. As a result, three chiral centers have been efficiently constructed.

Scheme 2



Reagents: a) $NaBH_4/CeCl_3$/MeOH; b) AcOH; c) *m*-CPBA/ CH_2Cl_2; d) PCC; e) AIP/*i*-PrOH; f) $O_3/CH_2Cl_2/Me_2S$; g) $NaBH_4$/MeOH, -78°C; h) $HS(CH_2)_3SH$/ $BF_3.OEt_2$ /CH_2Cl_2.

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