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Synthetic Studies of an Analogue of HIV-1 Protease Inhibitors of Didemnaketals: Construction of the C1-C8 Intermediate

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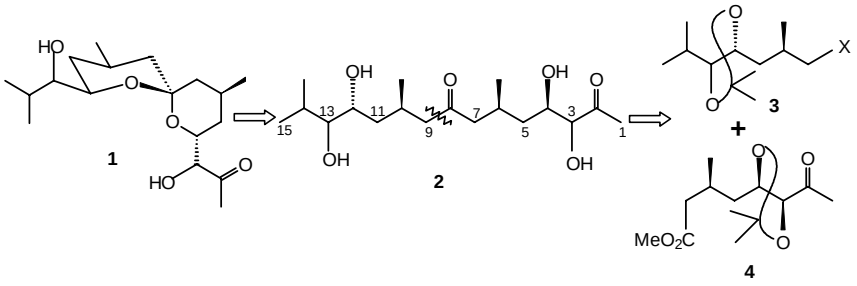
Abstract: A convenient and stereoselective approach to the synthesis of (3*S*, 4*R*, 6*S*)- 2–oxo–3, 4-dihydroxy-6–methyl-octanate derivative, a key intermediate for the synthesis of HIV-1 protease inhibitor of didemnaketals analogue, has been developed successfully from L-(-)-menthone.

Keywords: Didemnaketals, 2–oxo–3, 4-dihydroxy-6–methyl-octanate, steroselective synthesis.

The didemnaketals A and B have proved to be significant inhibitors to HIV-1 protease[1]. Up to the present, however, no successful synthesis has been reported. In connection with our synthetic studies of their analogues, we have reported a successful synthesis of the similar intermediate of **3**[2]. Herein we would present an efficient procedure for the diastereoselective synthesis of another intermediate **4**.

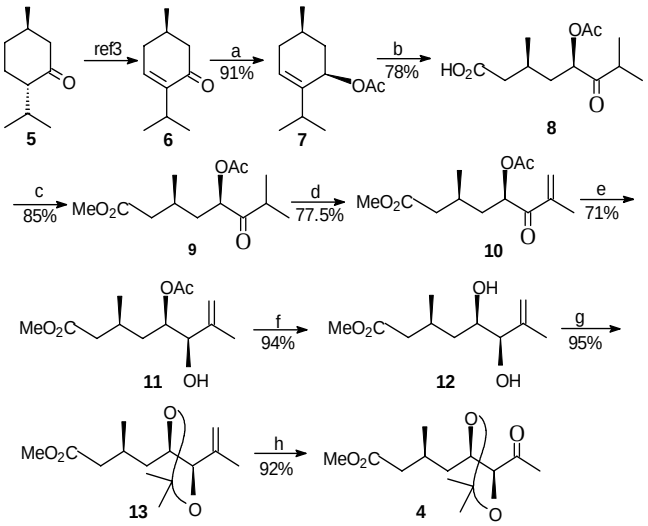
Scheme 1



Based on the retrosynthetic analysis, the intermediate **4** could be synthesized from natural L- (-)-menthone because of the valuable chiral C5 methyl. In addition, because the stereochemistry of C3 was not determined, we selected any one configuration for our initial synthetic studies. Therefore, as shown in **scheme 2**, menthone **6**, which was obtained conveniently by a literature method[3], was reduced with $NaBH_4$ and then protected with acetic anhydride to afford the only product **7**. After ozonization and successively oxidized with Jones reagent, **8** was given in high yield, which then was esterified with CH_3I / K_2CO_3 in acetone to give **9**. Bromination of **9** with NBS and then dehydrobromination with LiBr / Li_2CO_3 / DMF gave **10**. Treatment of **10** with $NaBH_4$ at –40°C gave the isomer **11** together with 26% 3-epimer. Compound **11** was

hydrolyzed with K_2CO_3 / MeOH to afford **12**. After protection of **12** with acetone and then ozonization, the final compound **4** was obtained as a colorless oil in high yield[4]. The structures of all these compounds above were determined by NMR, MS, HRMS and the configuration was confirmed by NOESY technique. The complete synthesis of the compound **1** is on going and will be reported in the near future.

Scheme 2



Reagents and conditions: a. $NaBH_4$ / MeOH, then Ac_2O / Py; b. O_3 / CH_2Cl_2, Et_3N, then Jones reagent; c. CH_3I / K_2CO_3 / Acetone; d. NBS, CCl_4, reflux, then LiBr / Li_2CO_3 / DMF, reflux; e. $NaBH_4$ / MeOH; f. K_2CO_3 / MeOH; g. Acetone / PTS; h. O_3 / CH_2Cl_2, then Zn / HOAc.

References and notes

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4 The spectral data of compound 4 were submitted to Editorial Department of CCL.

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