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Synthesis of a Hydroxylated Muricatacin Analog related to Squamocin

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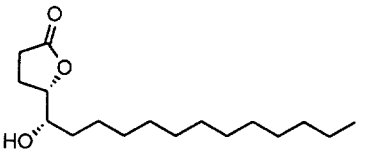
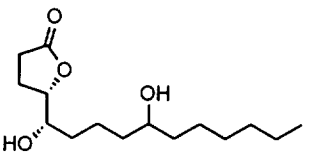
Abstract:: Compound **1** was synthesized in 9 steps and 5.5% overall yield from heptanal. The IC_{50} of compound **1** against the growth of human hepatocarcinoma cell lines (Hep G_2 and 2,2,15) are 22.0 and 21.8 μM, respectively.

The rapidly growing family of Annonaceous acetogenins have attracted much interest because of their wide range of biological activity and unique structure.[1] Muricatacin has been isolated from the seeds of *Annona muricata*, shows cytotoxic activity on tumor cell lines,[2] and it is probably a product of oxidative cleavage of monotetrahydrofuranic acetogenins and a precursor for the synthesis of various biologically active acetogenins.[3] Compound **1** was designed as a hydroxylated analog of muricatacin. Although it is not known in nature, it could be a precursor or metabolite of acetogenins, such as squamocin[4] and asminacin.[5] By the synthesis of compound **1**, it would allow us to compare its biological activity with muricatacin and analogs with human tumor cell lines to establish a structue-activity relationship. Furthermore, **1** may serve as a useful building block for the synthesis of Annonaceous acetogenins.



muricatacin



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The synthesis of compound **1** is outlined in Scheme 1. The tetrahydropyranyl protected 3-butyn-1-ol (**2**) was treated with butyllithium at -78 °C, then heptanal, and after acidic workup, gave ynol **3** in 82% yield. Hydrogenation of **3** using nickel boride catalyst[6] and 2 equiv. of hydrogen gave alcohol **4** in 76% yield. Compound **4** was converted into the *O*-benzyl derivative **5** in 85% yield by treatment of **4** with sodium hydride, benzyl bromide and tetrabutyl ammonium iodide in N,N-dimethylforamide.[7] The tetrahydropyranyl group was removed by treatment of **5** with camphor sulfonic acid in methanol to give alcohol **6** in 73% yield. Oxidation of alcohol **6** with pyridinium chlorochromate in dichloromethane afforded aldehyde **7** in 65% yield. Reaction of **7** with vinyl magnesium bromide in tetrahydrofuran at -78 °C gave allylic alcohol **8** in 50% yield as a 1:1 mixture of diastereomers. Compound **8** was then treated with ethyl orthoacetate and propionic acid at 180 °C for 2 h[8] to give ester **9** in 91% yield. Ester **9** was treated with AD-mix-α in *tert*-butyl alcohol and water together with methanesulfonamide[8] to give **10** in 52% yield. Finally, the benzyl protecting group was removed by

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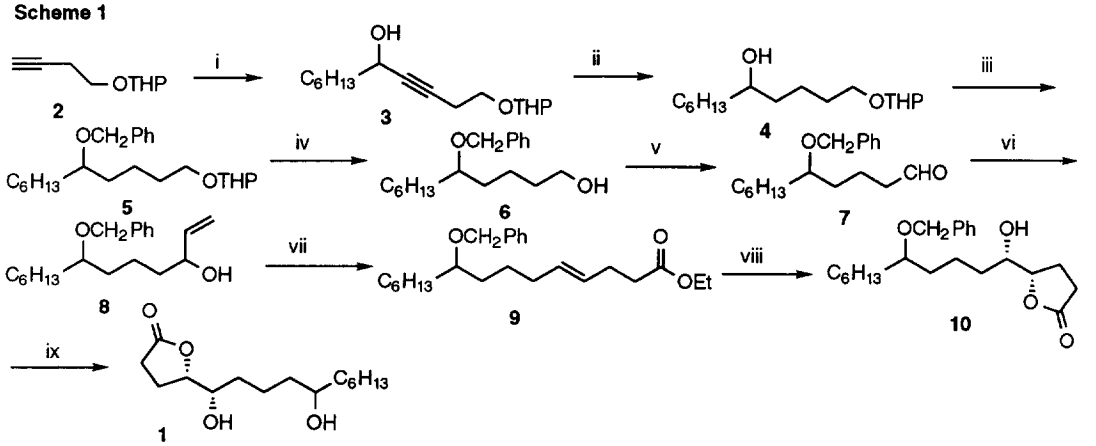
hydrogenation of **10** in ethanol using palladium charcoal as catalyst to give compound **1** in 91% yield. Compound **1** is obtained as a white solid, mp 57-59 °C, $[\alpha]_D^{25}$ +19.8 (c 0.72, $CHCl_3$). ^1H and ^{13}C NMR indicated that compound **1** is a 1:1 mixture of two diastereomers.

Scheme 1



Reagents and Conditions: i) nBuLi, THF, -78 °C, 1 h; then heptanal, -78 °C, 2 h, 82%; ii) Ni_2B, 2 H_2, EtOH, 76%; iii) NaH, $PhCH_2Br$, Bu_4NI, DMF, 25 °C, 6 h, 86%; iv) CSA, CH_3OH, 25 °C, 6 h, 73%; v) PCC, CH_2Cl_2, 25 °C, 1.5 h, 65% vi) vinyl magnesium bromide, THF, -78 °C, 4 h, 50%; vii) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, 180 °C, 2 h, 91%; viii) AD-mix-α, $CH_3SO_2NH_2$, tBuOH, H_2O, 0 °C, 24 h, 52%; ix) H_2, Pd/C, EtOH, 12 h, 91%.

Without separation of these two diastereomers, the activity of compound **1** was evaluated *in vitro* against two human hepatocarcinoma cell lines (Hep G_2 and 2,2,15). Dose response curves for each cell line were measured at five different drug concentrations. The concentrations causing 50% cell growth inhibition (IC_{50}) compared with the control were calculated. The IC_{50} of compound **1** against the growth of Hep G_2 and Hep G_2 transfected hepatitis B virus (2,2,15) cancer cell lines are 22.0 and 21.8 μM, respectively. The IC_{50} of muricatacin against the growth of these two cancer cell lines are 14.9 and 18.0 μM, respectively.

In conclusion, we have developed an efficient and a general method to synthesize a hydroxylated muricatacin analog. The application of this method to synthesize a variety of hydroxylated muricatacin analogs is cuurently under investigation. The results and biological activities of these analogs will be reported in due course.

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