

Synthesis of a Hydroxylated Muricatacin Analog related to Squamocin

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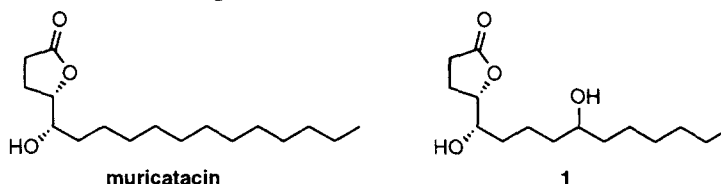
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Abstract: Compound **1** was synthesized in 9 steps and 5.5% overall yield from heptanal. The IC₅₀ of compound **1** against the growth of human hepatocarcinoma cell lines (Hep G2 and 2.2.15) are 22.0 and 21.8 μ M, respectively.

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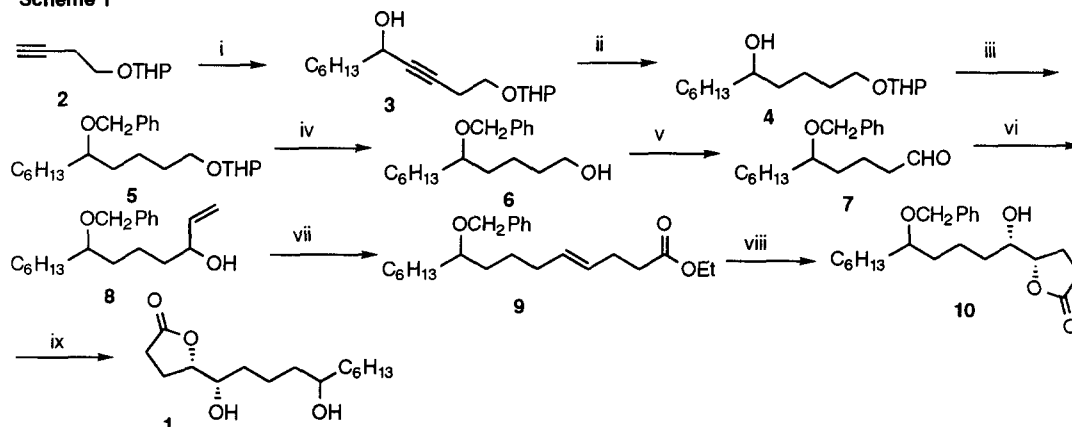
The rapidly growing family of Annonaceous acetogenins have attracted much interest because of their wide range of biological activity and unique structure.¹ Muricatacin has been isolated from the seeds of *Annona muricata*, shows cytotoxic activity on tumor cell lines,² and it is probably a product of 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 squamocin⁴ 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 structure-activity relationship. Furthermore, **1** may serve as a useful building block for the synthesis of Annonaceous acetogenins.



The synthesis of compound **1** is outlined in Scheme 1. The tetrahydropyranyl protected 3-buten-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 catalyst⁶ 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*-dimethylformamide.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 h⁸ to give ester **9** in 91% yield. Ester **9** was treated with AD-mix- α in *tert*-butyl alcohol and water together with methanesulfonamide⁸ to give **10** in 52% yield. Finally, the benzyl protecting group was removed by

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, CHCl₃). ¹H and ¹³C 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) Ni₂B, 2 H₂, EtOH, 76%; iii) NaH, PhCH₂Br, Bu₄NI, DMF, 25 °C, 6 h, 86%; iv) CSA, CH₃OH, 25 °C, 6 h, 73%; v) PCC, CH₂Cl₂, 25 °C, 1.5 h, 65%; vi) vinyl magnesium bromide, THF, -78 °C, 4 h, 50%; vii) CH₃C(OEt)₃, CH₃CH₂CO₂H, 180 °C, 2 h, 91%; viii) AD-mix-α, CH₃SO₂NH₂, tBuOH, H₂O, 0 °C, 24 h, 52%; ix) H₂, 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 G₂ 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 (IC₅₀) compared with the control were calculated. The IC₅₀ of compound **1** against the growth of Hep G₂ and Hep G₂ transfected hepatitis B virus (2,2,15) cancer cell lines are 22.0 and 21.8 μM, respectively. The IC₅₀ 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 currently under investigation. The results and biological activities of these analogs will be reported in due course.

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References and Notes:

1. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, 275.
2. Rieser, M. J.; Koslowski, J. F.; Wood, K. V.; McLaughlin, J. L. *Tetrahedron Lett.* **1991**, 32, 1137.
3. Figadere, B. *Acct. Chem. Res.* **1995**, 28, 359.
4. (a) Fujimoto, Y.; Eguchi, T.; Kakinuma, K.; Ikekawa, N.; Sahai, M.; Gupta, Y. *Chem. Pharm. Bull.* **1988**, 36, 4802. (b) Gypser, A.; Bulow, C.; Scharf, H.-D. *Tetrahedron* **1995**, 51, 1921.
5. Zhao, G.-X.; Miesbauer, L. R.; Smith, D. L.; McLaughlin, J. L. *J. Med. Chem.* **1994**, 37, 1971.
6. Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* **1969**, 1837.
7. Kanai, K.; Sakamoto, I.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1987**, 60, 1529.
8. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, 92, 741.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Am. Chem. Soc.* **1992**, 114, 2768.