

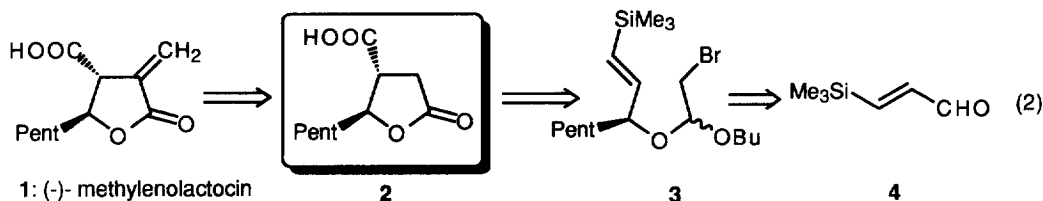
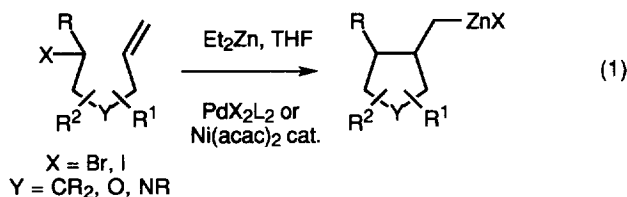
A Short Formal Synthesis of (-)-Methylenolactocin via a Nickel Catalyzed Intramolecular Carbozincation

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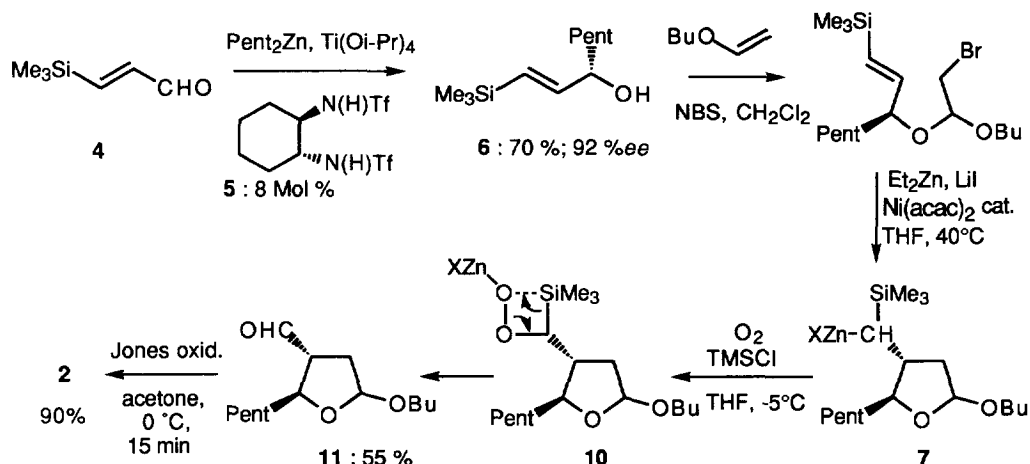
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Summary: The lactone **2** which can be converted in one step into (-)-methylenolactocin **1** was prepared in 4 steps, 30 % overall yield and > 92 % ee starting from (E)-3-trimethylsilylpropenal **4**. The key step is a new nickel catalyzed cyclization of the polyfunctional bromo-alkenylsilane **3** mediated by Et₂Zn. The intermediate organozinc species **7** has been directly oxidized to an aldehyde with oxygen.

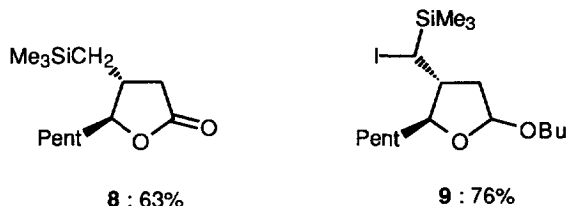
Recently, we have developed a new radical cyclization of polyfunctional 5-hexenyl halides mediated by Et₂Zn and catalyzed by nickel or palladium salts.¹ The reaction tolerates the presence of a broad range of functionalities in the cyclization precursors and produces polyfunctional 5-membered carbo- and hetero-cycles with excellent stereoselectivity (Eq. 1).¹ Herein, we wish to report an application of this reaction to the synthesis of the antitumor antibiotic (-)-methylenolactocin **1** which has been synthesized previously by Greene.² We describe a short enantioselective synthesis of the functionalized lactone **2** by the cyclization of **3** starting from (E)-3-trimethylsilylpropenal^{3,4} **4** (Eq. 2). The lactone **2** has been converted in one step to **1**.²



Addition of Pent₂Zn (2 equiv) to the aldehyde **4** in the presence of the chiral catalyst **5** and Ti(Oi-Pr)₄ (2 equiv) produces the allylic alcohol **6** in 70 % yield and 92 % ee (toluene, -30 to 0 °C, 4h).⁴ The reaction of **6** with butyl vinyl ether and N-bromosuccinimide in CH₂Cl₂ (0 °C, 1h) affords the bromoacetal **3** in 88 % yield. The nickel catalyzed cyclization of **3** proceeds smoothly at 40 °C in THF in the presence of LiI (0.25 equiv) and a catalytic amount (5 mol%) of Ni(acac)₂ (40 °C, 12 h). The resulting zinc reagent **7** gives after protonation and oxidation with MCPBA and BF₃·OEt₂ (15 mol %) (CH₂Cl₂, 25 °C, 0.5 h)⁶, the *trans*-



lactone **8** (63 % yield, 100 % *trans*), showing the high stereoselectivity of the cyclization. The iodolysis of **7** provides the iodide **9** in 76 % yield. The direct oxidation of **7** with oxygen⁷ in the presence of TMSCl (2 equiv) affords via the intermediate zinc peroxide **10** the acetal **11** (THF, -5 °C, 3–4 h) in 55 % overall yield. Jones oxidation of **11** leads to the pure *trans*-lactone **2** (acetone, 0 °C, 15 min, 90 % yield). This crystalline compound has a melting point of 104 °C (mp(lit.)⁸: 105–107°C) and a specific rotation of $[\alpha]_D = -50.5$ (c 0.41, CHCl₃); $([\alpha]_D)_{lit} = -54$ (c 0.4, CDCl₃).⁸



In summary, we have prepared the lactone **2** in 4 steps, 30 % overall yield and > 92 % *ee*, demonstrating the efficiency of the nickel catalyzed cyclization¹ and showing the synthetic potential of the direct oxygen oxidation of zinc organometallics.

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