

Chiral Synthesis of the Key Intermediate of Diterpenoids

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Abstract: (-)-Methyl(4*R*, 5*S*, 10*R*)-14-methoxypodocarpa-8, 11, 13-triene-19-oate(1), which is the key intermediate for synthesis of diterpenoids, was synthesized from (*R*)-(+)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone(2).

(-)-Methyl(4*R*, 5*S*, 10*R*)-14-methoxypodocarpa-8, 11, 13-triene-19-oate(1) is the key intermediate for syntheses of diterpenoids such as kaurenoic acid(3), kaur-16-en-19-ol(4), monoginol(5)⁽¹⁾, as well as C₂₀-diterpene alkaloids such as veachine (6), garryine(7) and atisine(8)⁽²⁾. The racemic synthesis of this intermediate was done by K.Mori *et al*⁽³⁾, but the chiral synthesis has not been reported. Here we present the chiral synthesis of this key intermediate from (*R*)-(+)-2-methyl-2-(2'-nitrovinyl)- δ -valerolactone(2).

2 was synthesized according to literature method⁽⁴⁾ with 95% yield and 91% ee. The Michael addition of 2 with 2-(2'-methoxyphenyl)-ethyl magnesium bromide(9) afforded a mixture(1:1) of 10 in 82% yield. Without separation, the mixture was directly treated with NaOMe followed by mesylation and substitution with sodium iodide in acetone to give iodide 11 in 85% yield. Intramolecular alkylation of 11 and the successive Nef reaction with TiCl₃/NH₄OAc⁽⁵⁾ provided the desired 12a(H= β) and a minor isomer 12b(H= α) (6:1) in 42% overall yield. 12a and 12b were shown to reach an equilibrium in the ratio of 1:1 with *p*-TsOH in MeOH or with NaOMe in MeOH. 12a was treated with Zn/TiCl₄/CH₂Br₂⁽⁶⁾ at room temperature to provide methylenation product 13. Unlike the case of synthesis of podocarpic acid⁽⁷⁾, the Friedel-Crafts cyclization of 13 was difficult because lactonation of 13 is very easy. Mori's method⁽³⁾ afforded cyclic product (1) in only 1.2% yield, while Eaton reagent⁽⁸⁾ provided over four products with only 20% desired compound 1. It is better when 13 was treated with MeSO₃H in CH₂Cl₂ to give (-)-methyl (4*R*,5*S*,10*R*)-14-methoxypodocarpa-8,11,13-triene-19-oate (1) in 62% yield.

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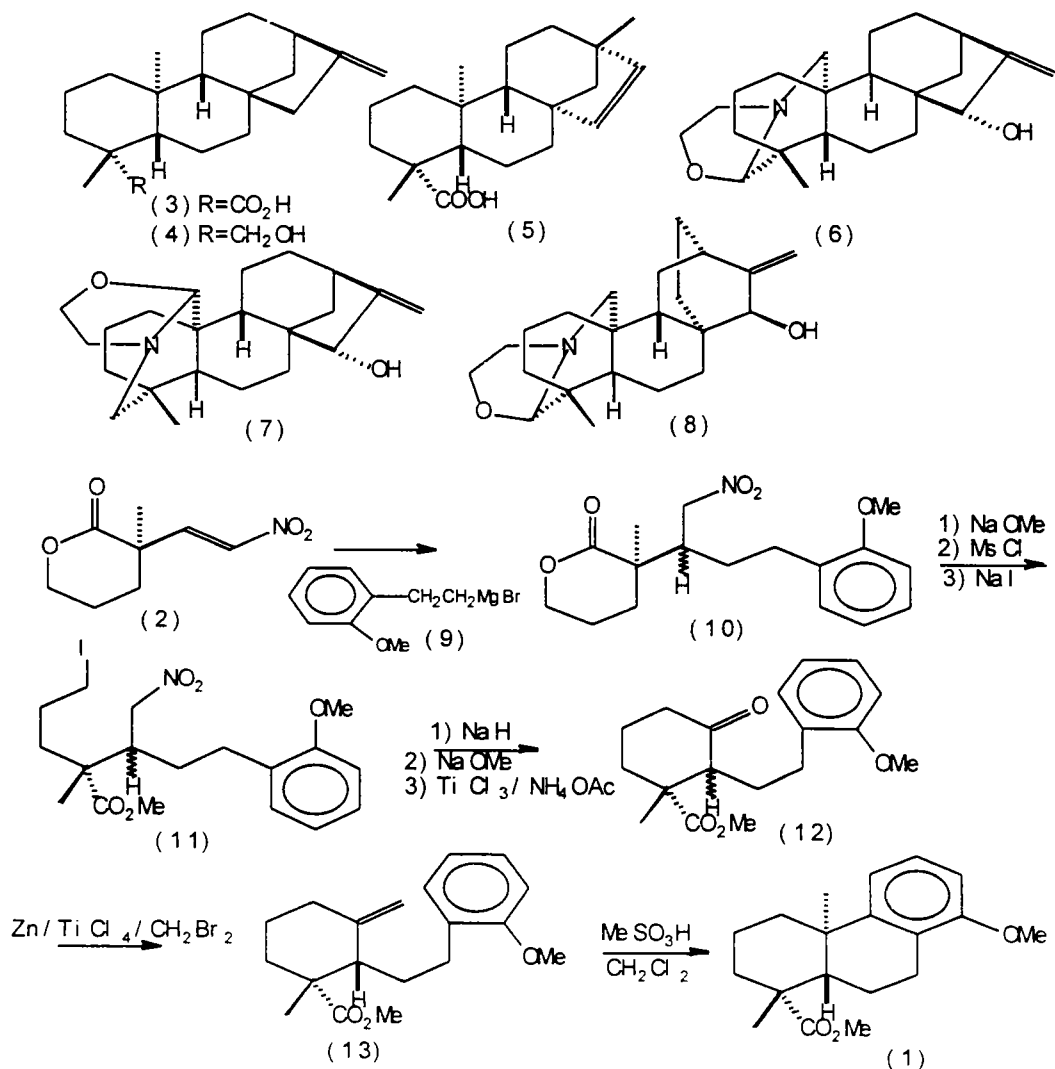
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