

Efficient Total Syntheses of (±)Protolichesterinic Acid and (±)Rocellaric Acid via Tungsten- π -allyl Complexes

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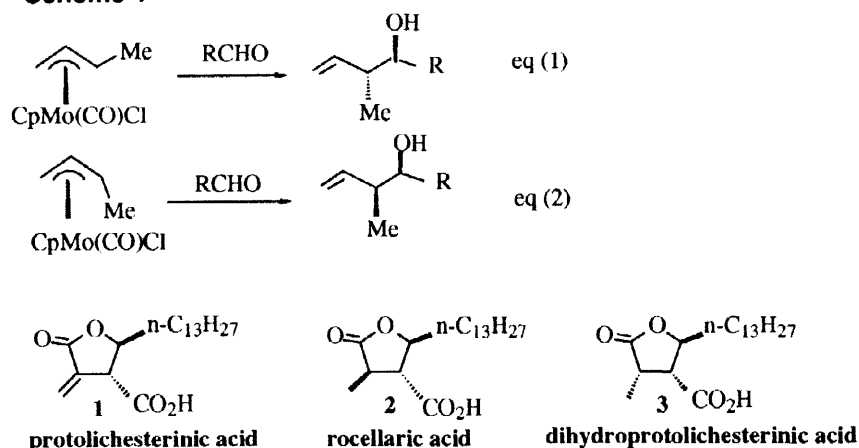
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Abstract: Total syntheses of racemic protolichesterinic acid (**1**) and rocellaric acid (**2**) were achieved with the use of tungsten- π -allyl complex in the key step. In this synthetic route, compounds **1** and **2** were prepared in four and six steps respectively starting from readily available chloropropargyl derivatives.

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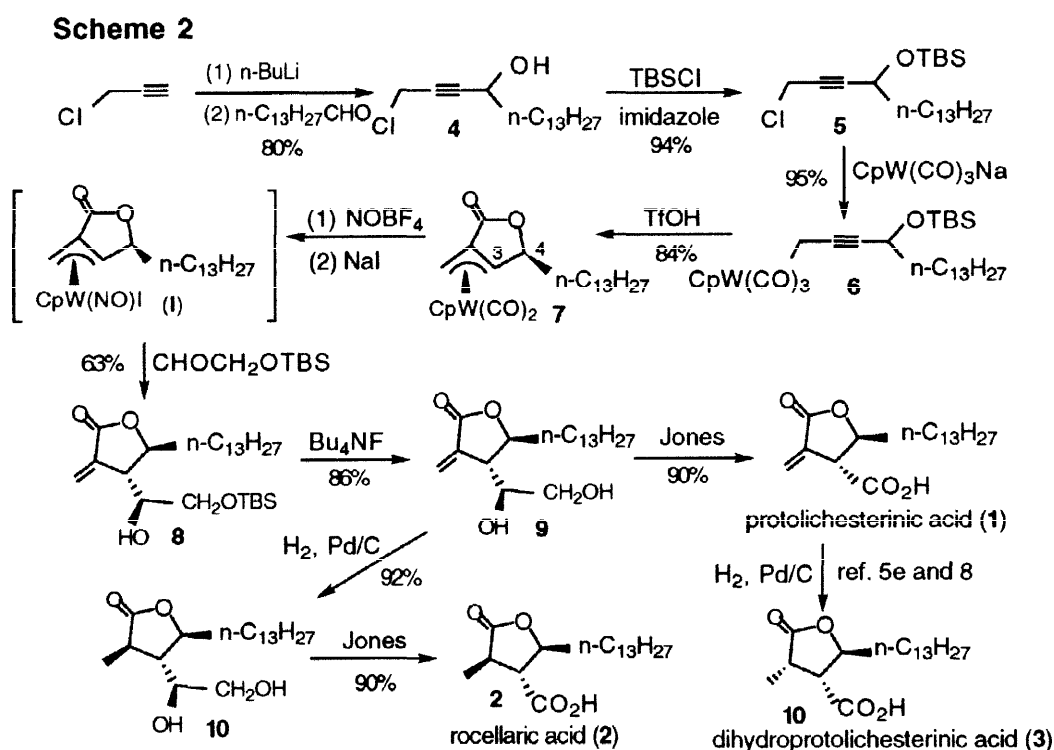
The synthesis of butenolides and saturated butyrolactones has received considerable attentions because of their wide occurrence in bioactive natural products.¹ These structural units are also useful building blocks for natural products such as alkaloids, macrocyclic antibiotics and pheromones.² Allylation of organic carbonyl compounds is a important method in organic synthesis.³ Fallér recently reported⁴ CpMo(NO)Cl(π -allyl) condensed with aldehydes via chairlike transition state, yielding homoallylic alcohols with excellent diastereoselectivities as shown in Scheme 1 (eqs 1-2). We applied this method to the syntheses of acyclic 1,3-diols, 1,3,5-triols and other oxygen heterocycles.⁵ Although synthetic application of these π -allyl complexes has received considerable attentions,⁶ the example to use these organometallics for the syntheses of natural compounds are very rare. Paraconic acids⁷ are a highly substituted type of bioactive γ -lactones in which the β -carbon of the lactone ring is occupied by a carboxylic acid; the prominent examples are protolichesterinic acid

Scheme 1



(1), rocellaric acid (2) and dihydroprotolichesterinic acid (3). In this paper, we report application of a single tungsten- π -allyl complex for efficient synthesis of these three natural paraconic acids.

Shown in Scheme 2 is our synthetic protocol which uses organotungsten compounds in the key step. The starting chloropropargyl derivative **5** was easily prepared in high yield (75%) from propargyl chloride, n -C₁₃H₂₇CHO and TBSCl (TBS=*tert*-butyldimethylsilyl).⁸ Metalation of compound **5** with CpW(CO)₃Na (1.0 equiv) in THF (23 °C, 12 h) proceeded smoothly to afford tungsten- η^1 -propargyl compound **6** in 95% yield. Subsequent treatment of this tungsten species **6** with triflic acid (0.20 equiv) in cold CH₂Cl₂ effected intramolecular alkoxy-carbonylation reaction to yield tungsten- π -allyl complex **7** in 84% yield. The *syn*-configuration of compound **7** is shown by the magnitude of coupling constant $J_{34} = 3.1$ Hz.^{5b} In this intramolecular cyclization, the TBS group of compound **6** is indispensable for the *syn*-stereoselection of tungsten- π -allyl complex **7**.^{5b} Sequential treatment of **7** with NOBF₄ and NaI in cold CH₃CN (0 °C) generated the corresponding CpW(NO)I(π -allyl) derivative (**I**)⁴ that was not isolated and used *in situ*. Complexes like (**I**) are known to be an allyl anion equivalent which reacts with electrophiles at its more substituted allyl carbon.⁴ Treatment of (**I**) with CHOCH₂OTBS *in situ* gave a 63% yield of *trans*- α -methylene butyrolactone **8** as a single stereoisomer. The *trans*-configuration of compound **8** was determined by ¹H NOE experiment. Although the CH(OH) configuration of γ -lactone **8** is not determined, the configuration is not crucial in our reaction sequence because it will be oxidatively cleaved to aldehyde in subsequent reactions. Desilylation of compound **8** was achieved via treatment of Bu₄NF in THF to give the diol **9** in 86% yield. Oxidative cleavage of the diol **9** was achieved smoothly on Jones oxidation⁹ to yield protolichesterinic acid **1** in



90% yield. Toward the synthesis of rocellaric acid **2**, compound **9** was treated with hydrogen (1 atm) over Pd/C catalyst (3 mol%) in MeOH (23 °C, 6 h) to give a 92% yield of saturated γ -lactone **10**. The *trans*-stereoselection of compound **10** is unusual because hydrogenation of β -substituted α -methylene butyrolactones tends to give a mixture of *cis* and *trans*-isomers.^{10,11} In this case, the diol substituent of **9** is presumably bound to palladium catalyst to control the stereochemistry of hydrogenation. The *trans*-configuration of compound **10** is determined by ¹H NOE experiment. Oxidative cleavage of the diol **10** by Jones oxidation produced rocellaric acid **2** in 90% yield. Spectral data of these two natural lactones **1** and **2** were identical to those of authentic samples.^{7a-e} The availability of protolichesterinic acid **1** is also accessible to another natural γ -lactone, *i.e.* dihydroprotolichesterinic acid **3** by direct hydrogenation on Pd/C catalyst according to reported procedures.^{7e,11}

In summary, we develop a short and divergent synthesis of three natural γ -lactones **1-3** with elaboration of a single tungsten- π -allyl complex **7**. The overall synthetic scheme is highly efficient among the published methods⁷, and it is applicable to other congeners. This work highlights the use of tungsten- π -allyl complexes in the syntheses of natural products.

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