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

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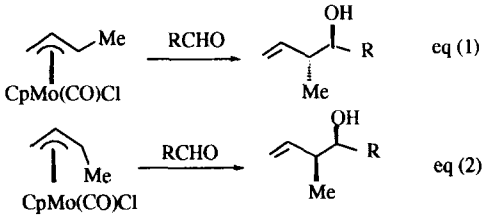
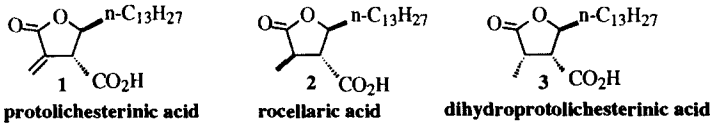
Abstract: Total syntheses of racemic protolichesterinic acid (**1**) and rocellaric acid (**2**) were achieved with the use of tungsten-π-allyl complex in the key step. In this synthetic route, compounds **1** and **2** were prepared in four and six steps respectively starting from readily available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

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] Faller recently reported[4] 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 heterocyclics.[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 acids[7] 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





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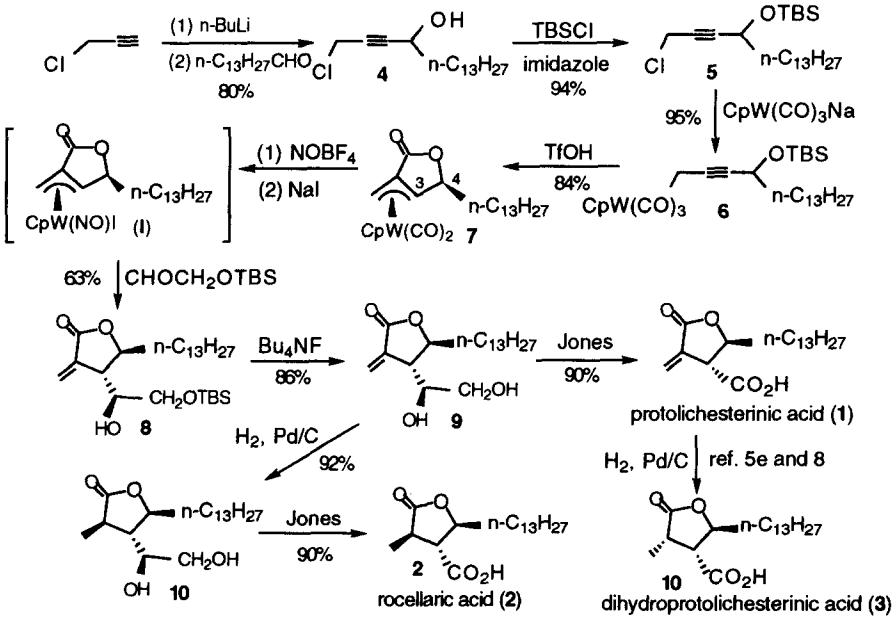
(**1**), rocellaric acid (**2**) and dihydroprotolichesterinic acid (**3**). In this paper, we report application of a single tungsten-π-allyl complex for efficient synthesis of these three natural paraconic acids.

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-$C_{13}H_{27}CHO$ and TBSCl (TBS=*tert*-butyldimethylsilyl).[8] Metalation of compound **5** with $CpW(CO)_3Na$ (1.0 equiv) in THF (23 ^{0}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 CH_2Cl_2 effected intramolecular alkoxycarbonykation reaction to yield tungsten-π-allyl complex **7** in 84% yield. The *syn*-configuration of compund **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 $NOBF_4$ and NaI in cold CH_3CN (0 ^{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 $CHOCH_2OTBS$ 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 ^{1}H NOE experiment. Although the *C*H(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 Bu_4NF in THF to give the diol **9** in 86 % yield. Oxidative cleavage of the diol **9** was achieved smoothly on Jones oxidation[9] to yield protolichesterinic acid **1** in

Scheme 2



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 ^{0}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 presumbly bound to palladium catalyst to control the stereochemistry of hydrogenation. The *trans*-configuration of compound **10** is determined by ^{1}H 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 methods[7], 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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