

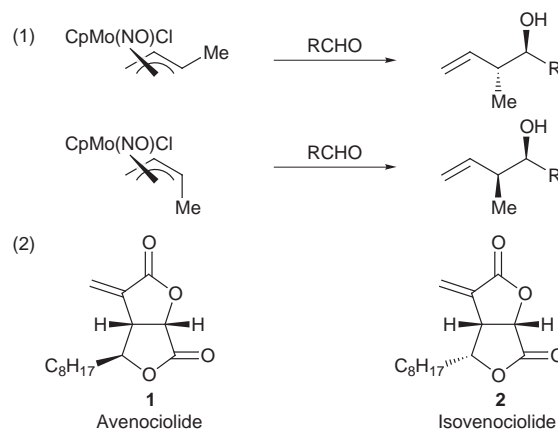
An efficient method for total syntheses of avenaciolide and isoavenaciolide *via* tungsten- π -allyl complexes

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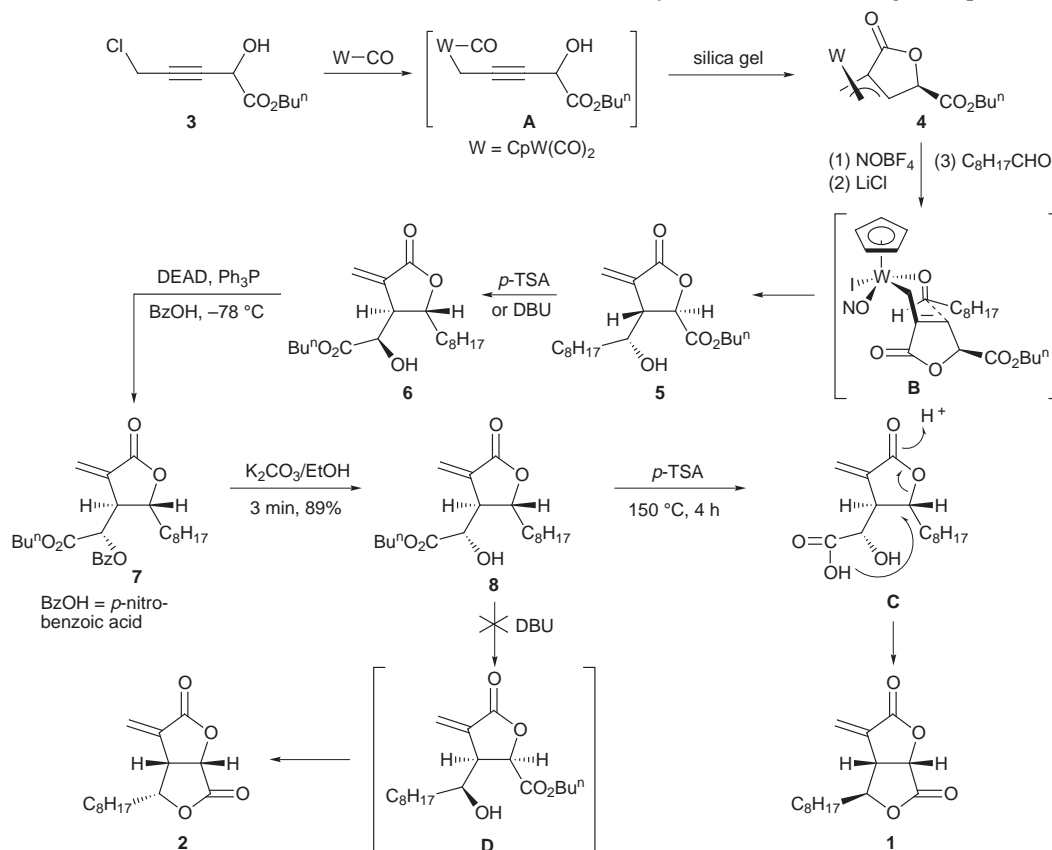
Total syntheses of avenaciolide and isoavenaciolide were achieved in six and three steps respectively based on starting chloropropargyl derivatives; the key step in such syntheses involves intramolecular alkoxy-carbonylation of tungsten- η^1 -propargyl complexes.

There has been increasing interest in the utilization of molybdenum- or tungsten- π -allyl compounds for organic syntheses.^{1,2} Faller *et al.* reported³ that $\text{CpMo}(\text{NO})\text{Cl}(\eta^3\text{-allyl})^3$ condensed with aldehydes *via* a chairlike transition state, yielding homoallylic alcohols with excellent diastereoselectivities (Scheme 1). We applied this method to the syntheses of acyclic 1,3-diols, 1,3,5-triols and other oxygen heterocycles.⁴ Despite numerous studies on these π -allyl species, there is no precedent for the synthesis of natural products based on these organometallics. Avenaciolide **1** and isoavenaciolide **2** are secondary metabolites isolated from *Aspergillus* and *Penicillium*; total syntheses of these two compounds have attracted considerable attention^{4,5} because of their diverse and potent biological activities. In this paper, we report total syntheses of these two bislactones based on tungsten- π -allyl complexes; this synthetic protocol is highly efficient because only a few steps are required from the starting chloropropargyl derivatives **3** and **9**.

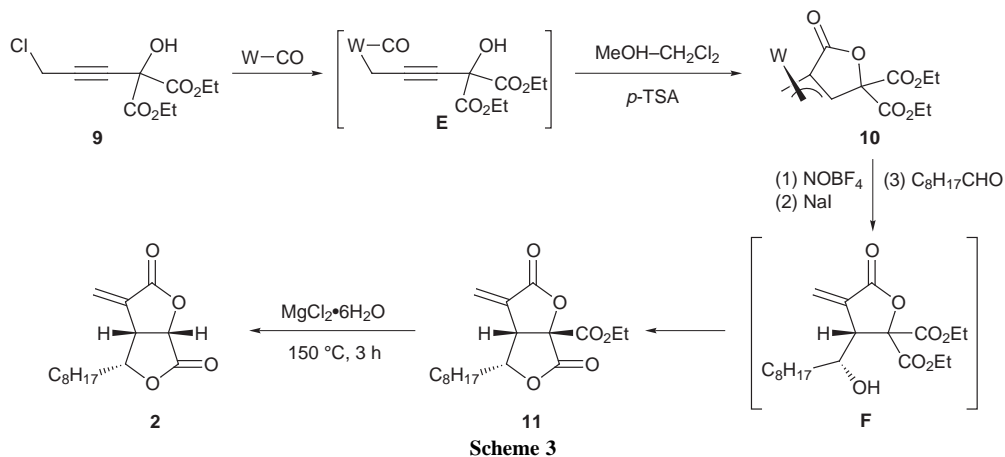


Scheme 1

The starting compound **3** is readily available from propargyl chloride and *n*-butylglyoxalate.⁶ As shown in Scheme 2, treatment of **3** with $\text{CpW}(\text{CO})_3\text{Na}$ (1.3 equiv.) yielded tungsten- η^1 -propargyl complex **A** which was not isolated due to its high reactivity. Elution of this tungsten species through a silica



Scheme 2



column induced intramolecular alkoxy carbonylation^{4a,b} to yield tungsten- π -allyl complex **4** in 70% yield. The *syn*-configuration of **4** is indicated by the coupling constant $J_{34} = 3.1$ Hz.^{4a,b} Sequential treatment of **4** with NOBF₄ (1.0 equiv.) and LiCl (2.0 equiv.) in CH₃CN generated an allyl anion equivalent³ that reacted with C₈H₁₇CHO to yield α -methylene butyrolactone **5** in 62% isolated yield. The *trans*-configuration of **5** was confirmed by a proton NOE experiment. Determination of the remaining CH(OH)C₈H₁₈ configuration relies on its transacylation product **6**. The stereochemistry of **5** can be rationalized based on a chairlike transition structure **B** in which the new carbon–carbon bond is formed opposite the CO₂Bu^u substituent. Although compound **5** has a structural skeleton like those for avenaciolide **1** and isoavenaciolide **2**, inversions of configuration of the C(5) and C(1') carbons and at the C(5) carbon of **5** are required to produce bislactones **1** and **2** respectively. Notably, epimerization at the C(5) carbon of **5** is expected to give isoavenaciolide **2**. Toward this direction, compound **5** was heated in toluene for 7 hours with the DBU catalyst (0.30 equiv.), however transacylation occurred to yield a new α -methylene butyrolactone **6** in 86% yield that also has a *trans*-configuration. Under the same conditions, the *p*-TSA (*p*-toluenesulfonic acid) catalyst (0.20 equiv.) also gave compound **6** in 91% yield. Hence, we sought to invert the configuration at the CH(OH) carbon of **6**; this was achieved by the Mitsunobu reaction,⁷ sequentially giving **7** and **8** in 90% and 89% yields respectively. Heating **8** with excess *p*-TSA·H₂O (2.0 equiv.) in toluene in a sealed tube (150 °C, 4 h) produced the desired avenaciolide **1** in 62% yield together with isoavenaciolide **2** in 5% yield. The generation of **1** can be envisaged to proceed from intramolecular attack of the acid group of **8** at its C(5) carbon to invert its stereoconfiguration,^{5c,d} ultimately yielding avenaciolide **1**. Attempts to synthesise isoavenaciolide **2** via base-catalyzed transacylation of compound **8** were unsuccessful. Heating a mixture of DBU (0.2–2.0 equiv.) and **8** in toluene at reflux for 72 h did not show any sign of chemical reaction, and the starting material **8** was recovered exclusively.

We sought to develop an alternative approach to the synthesis of isoavenaciolide **2** via tungsten- π -allyl complexes; the whole synthesis requires only a few steps from chloropropargyl species **9**.⁸ As shown in Scheme 3, treatment of **9** with CpW(CO)₃Na (2.0 equiv.) in THF at 23 °C gave the expected tungsten- η^1 -propargyl species **E** which was subsequently treated with *p*-TSA·H₂O (1.0 equiv.) in a MeOH–CH₂Cl₂ mixture (volume ratio = 1 : 10) to induce alkoxy carbonylation to yield tungsten- π -allyl complex **10** in 65% yield. Further conversion of **10** produced a π -allyl anion equivalent via

sequential treatment with NOBF₄ (1.0 equiv.) and NaI (2.0 equiv.), which then reacted with C₈H₁₇CHO (2.0 equiv.) via lactonization of the primary species **F**. Decarboxylation of **11** proceeded smoothly through heating its dimethylacetamide solution (150 °C, 3 h) containing MgCl₂·6H₂O (5.0 equiv.)⁹ to afford the desired isoavenaciolide **2** in 59% yield.

In summary, we report here the first example of the use of tungsten- π -allyl complexes for the efficient syntheses of naturally occurring compounds such as avenaciolide and isoavenaciolide. The overall synthetic scheme[†] is considered to be the most efficient of the known methods. This demonstration highlights the use of tungsten-allyl complexes in the syntheses of natural products.

Notes and References

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[‡] All the new compounds gave satisfactory microanalytical data.

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