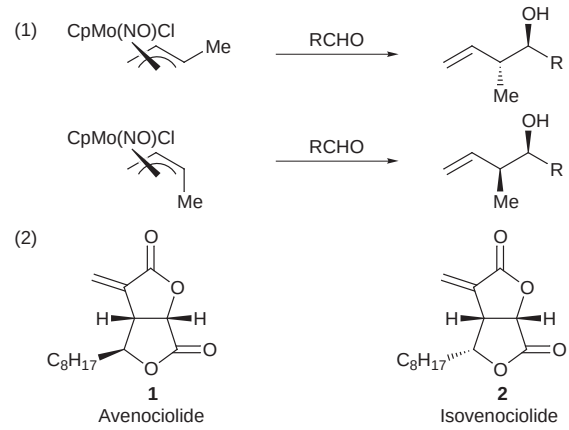
An efficient method for total syntheses of avenaciolide and isoavenaciolide *via* tungsten-π-allyl complexes

Kesavaram Narkunan and Rai-Shung Liu*†

Department of Chemistry, National Tsing-Hua University, Hsinchu, 30043, Taiwan, ROC

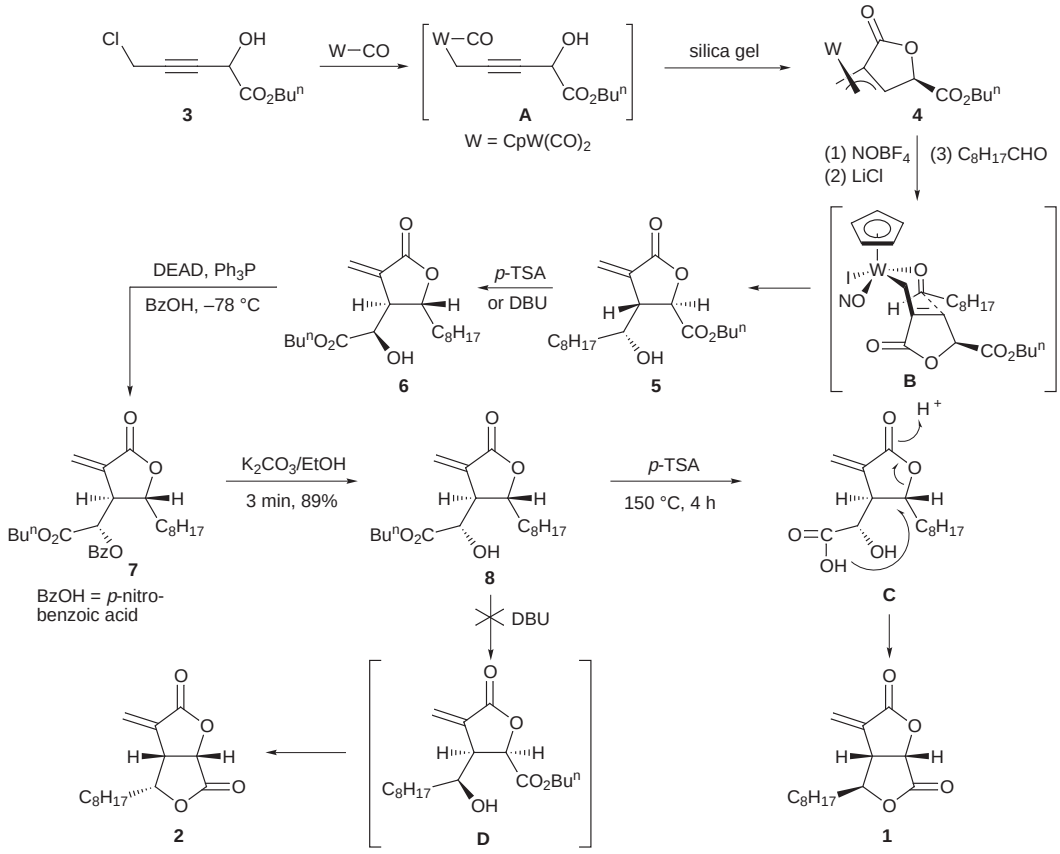
Total syntheses of avenaciolide and isoavenaciolide were achieved in six and three steps respectively based on starting chloropropargyl derivatives; the key step in such syntheses involves intramolecular alkoxycarbonylation of tungsten-η¹-propargyl complexes.

There has been increasing interest in the utilization of molybdenum- or tungsten-π-allyl compounds for organic syntheses.[1,2] Faller *et al.* reported[3] that CpMo(NO)Cl(η³-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**.

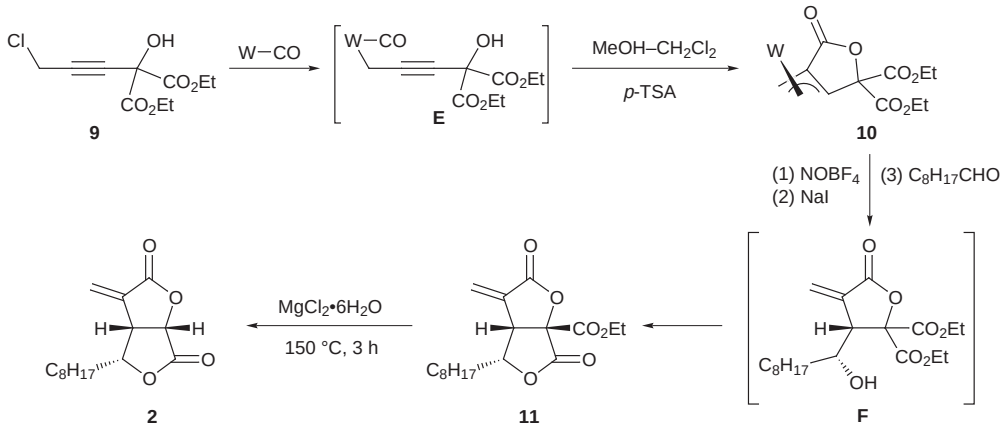


Scheme 1

The starting compound **3** is readily available from propargyl chloride and *n*-butylglyoxalate.[6] As shown in Scheme 2, treatment of **3** with $CpW(CO)_3Na$ (1.3 equiv.) yielded tungsten-η¹-propargyl complex **A** which was not isolated due to its high reactivity. Elution of this tungsten species through a silica



Scheme 2



Scheme 3

column induced intramolecular alkoxycarbonylation[4a,b] to yield tungsten-*syn*-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 $NOBF_4$ (1.0 equiv.) and LiCl (2.0 equiv.) in CH_3CN generated an allyl anion equivalent[3] that reacted with $C_8H_{17}CHO$ 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 $CH(OH)C_8H_{18}$ 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 CO_2Bu^n 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·H_2O (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·H_2O (1.0 equiv.) in a MeOH–CH_2Cl_2 mixture (volume ratio = 1 : 10) to induce alkoxycarbonylation to yield tungsten-π-allyl complex **10** in 65% yield. Further conversion of **10** produced a π-allyl anion equivalent *via* sequential treatment with $NOBF_4$ (1.0 equiv.) and NaI (2.0 equiv.), which then reacted with $C_8H_{17}CHO$ to yield a 62% yield of bislactone species **11** which was presumably produced *via* lactonization of the primary species **F**. Decarboxylation of **11** proceeded smoothly through heating its dimethylacetamide solution (150 °C, 3 h) containing $MgCl_2·6H_2O$ (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

† E-mail: rsliu@faculty.nthu.edu.tw

‡ All the new compounds gave satisfactory microanalytical data.

1 A. J. Pearson, *Synlett*, 1990, 10.
2 A. J. Pearson, in *Comprehensive Organometallic Chemistry*, ed. G. Wilkinson, F. G. A. Stone and E. W. Abel, Pergamon Press, Oxford, 1995, vol. 12, p. 637.
3 (*a*) J. W. Faller and D. L. Linebarrier, *J. Am. Chem. Soc.*, 1989, **111,** 1939; (*b*) J. W. Faller, J. A. John and M. R. Mazzier, *Tetrahedron Lett.*, 1989, **31**, 1769.
4 (*a*) W.-J. Vong, S.-M. Peng, S.-H. Peng, S.-H. Lin, W.-J. Lin and R.-S. Liu, *J. Am. Chem. Soc.*, 1991, **113**, 573; (*b*) C.-H. Chen, J.-S. Fan, G.-H. Lee, S.-M. Peng, S.-L. Wang and R.-S. Liu, *J. Am. Chem. Soc.*, 1995, **117**, 2933; (*c*) C.-H. Chen, J.-S. Fan, G.-H. Lee, S.-J. Shieh, S.-L. Wang, S.-M. Peng, S.-L. Wang and R.-S. Liu, *J. Am. Chem. Soc.*, 1996, **118,** 9279.
5 (*a*) S. Tsuboi, J.-I. Sakamoto, H. Yamashita, T. Sakai and M. Utaka, *J. Org. Chem.*, 1998, **63**, 1102; (*b*) W. L. Parker and F. Johnson, *J. Org. Chem.*, 1973, **38**, 2489; (*c*) C. M. Rodriguez, T. Martin and V. S. Martin, *J. Org. Chem.*, 1996, **61**, 8448; (*d*) S. D. Burke, G. J. Pacofsky and A. D. Piscopio, *J. Org. Chem.*, 1992, **57**, 2228; (*e*) J. H. Udding, K. J. M. Tuijp, M. N. A. Van Zanden, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1994, **59**, 1993.
6 L. Brandsma, in *Preparative Acetylenic Chemistry*, Elsevier, Amsterdam, 1988.
7 (*a*) L. E. Overman, K. L. Bell and F. Ito, *J. Am. Chem. Soc.*, 1984, **106**, 4192; (*b*) M. Okabe, R. C. Sun and G. B. Zenchoff, *J. Org. Chem.*, 1991, **56,** 4392.
8 Y. Nagao, K. Kim, S. Sano, H. Kakegawa, W. S. Lee, H. Shimizu, M. Shiro and N. Katunuma, *Tetrahedron Lett.*, 1996, **37,** 861.
9 J. A. J. M. Vekemans, C. W. M. Dapperens, R. C. Laessen, A. M. J. Koten and E. J. F. Chittenden, *J. Org. Chem.*, 1990, **55**, 5336.

Received in Cambridge, UK, 11th May 1998; 8/03491E