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# Total Synthesis of *Phytophthora* Mating Hormone α1

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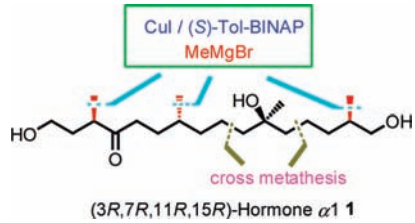
## ABSTRACT




**Total synthesis of *Phytophthora* mating hormone α1 (1) has been demonstrated. The required stereochemistries (methyl) are achieved by applying CuI-(*S*)-Tol-BINAP-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated esters.**

*Phytophthora* are mostly water molds that can extensively destroy important agricultures and cause high economical loss. Therefore, they are often considered as one of the most threatened phytopathogens in the world.[1] This can be seen from the Irish potato famine arising from phytopathogens that caused potato diseases, known as late blight, in the mid 1840s.[2] Interestingly, hormone α1 (**1**) (Figure 1) is found to be a universal mating hormone as it induces oospore formation not only in the A1 mating type of *P. nicotianae* but also in A2 mating types of *P. capsici*, *P. cambivora*, and *P. infestans*.[3] The isolation of hormone α1 was made possible from *P. nicotianae* by Ojika's group,[3] which has attracted tremendous interest among chemists.[4] Qin and co-workers first confirmed its absolute configuration and reported the total synthesis of **1**.[5] Almost at the same time, Feringa and co-workers have reported the synthesis of its enantiomer (**2**) and diastereomer (**3**) and evaluated their biological activities, independently.[6] Due to its fascinating hormone structure and biological activities, our group has been interested in the total synthesis of (3*R*,7*R*,11*R*,15*R*)-hormone α1 (**1**).

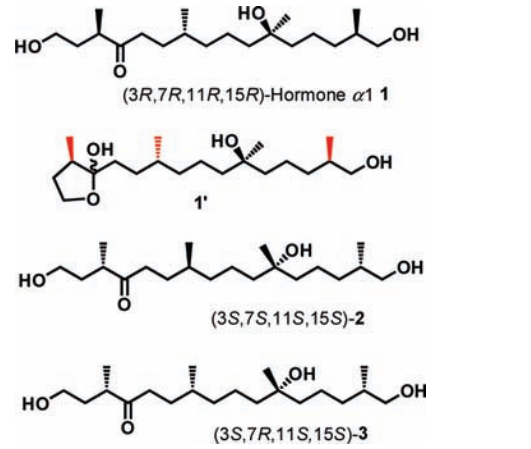



**Figure 1.** Structures of *Phytophthora* mating hormone α1 **1**, its hemiacetal **1′**, enantiomer **2**, and diastereomer **3**.

[†] S.-Y. Wang and P. Song have made equal contributions to this paper.

(1) Andrivon, D. *Plant Pathol.* **1996**, *45*, 1027–1035.
(2) Fry, W. E.; Goodwin, S. B. *Bioscience* **1997**, *47*, 363–371.
(3) Qi, J.; Asano, T.; Jinno, M.; Matsui, K.; Atsumi, K.; Sakagami, Y.; Ojika, M. *Science* **2005**, *309*, 1828–1828.
(4) For synthesis and biological activities of the stereoisomeric mixture of **1**, see: (a) Yajima, A.; Kawanishi, N.; Qi, J.; Asano, T.; Sakagami, Y.; Nukada, T.; Yabuta, G. *Tetrahedron Lett.* **2007**, *48*, 4601–4603. (b) Ojika, M.; Qi, J.; Kito, Y.; Sakagami, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 1763–1765. (c) Ojika, M.; Qi, J.; Kito, Y.; Sakagami, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 2497–2497. (d) Bajpai, R.; Yang, F.; Curran, D. P. *Tetrahedron Lett.* **2007**, *48*, 7965–7968.

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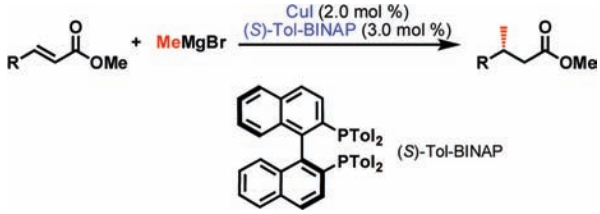
Recently, our group has developed a highly enantioselective method using CuI-Tol-BINAP-catalyzed conjugate addition of Grignard reagents to α,β-unsaturated esters to afford the desired β-methyl-substituted methyl ester with excellent enantioselectivity (Scheme 1).[7,8] In this report, application

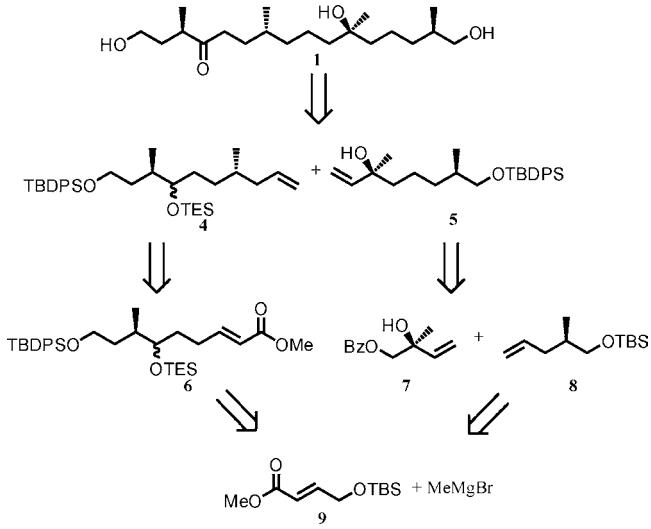
**Scheme 1.** General Strategy to the Synthesis of Chiral β-Methyl Esters




of this method to the synthesis of (3*R*,7*R*,11*R*,15*R*)-hormone α1 (**1**) will be expounded.

The key steps of our total synthesis of hormone α1 (**1**) involve the assembly of the two fragments **4** and **5** by cross-metathesis reaction (Scheme 2).[9] The fragment **4**, in turn,

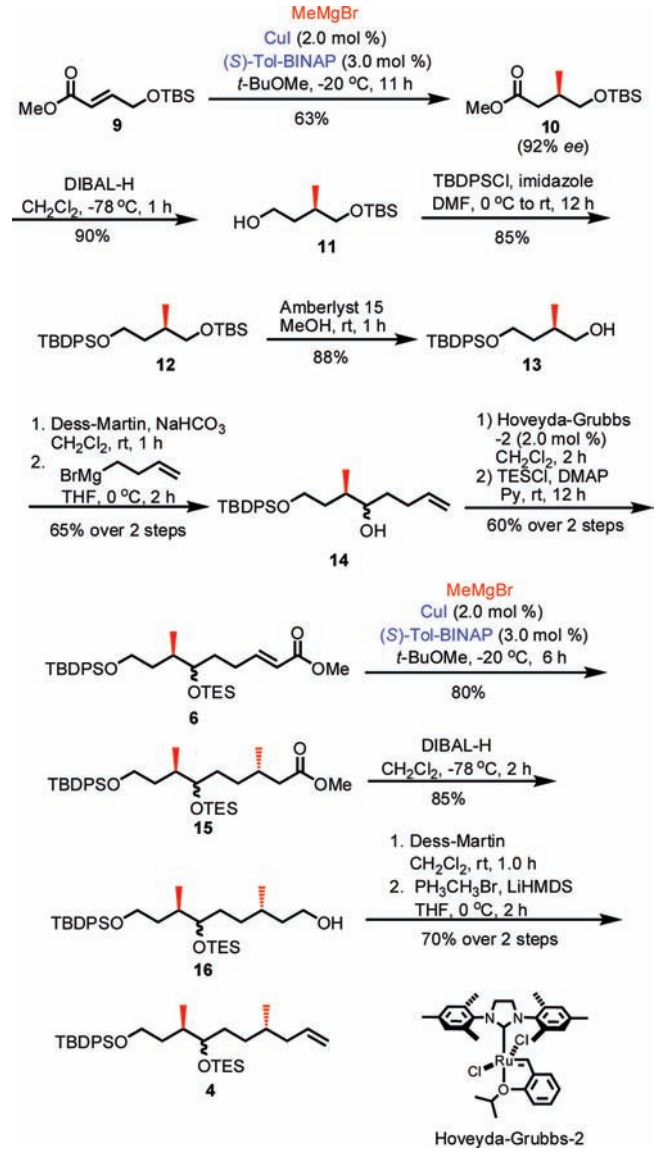
**Scheme 2.** Retrosynthetic Analysis of **1**




can be obtained by two iterative CuI-(*S*)-Tol-BINAP-catalyzed conjugate additions of MeMgBr to **9**. The fragment **5** can be generated via cross-metathesis reaction of **7** and **8**. **8** also can be obtained from the CuI-(*S*)-Tol-BINAP-catalyzed conjugate addition of MeMgBr to **9**.

The total synthesis of hormone α1 (**1**) started from 1,4-conjugate addition (CA) of MeMgBr to α,β-unsaturated ester **9** catalyzed by CuI-(*S*)-Tol-BINAP (Scheme 3). The desired

**Scheme 3.** Synthesis of **4**




ester **10** was obtained in 63% yield with 92% ee. A simple DIBAL-H reduction furnished the primary alcohol **11**, which was then protected with TBDPS to yield **12**. TBS was selectively deprotected, and the resulting primary alcohol **13** was allowed to react with Dess−Martin reagent to afford the aldehyde intermediate. Freshly prepared but-3-enylmagnesium bromide was injected smoothly to the aldehyde leading to a mixture of diastereomers **14** (dr = 58:42). Following cross-metathesis with methyl acrylate using second-generation Hoveyda−Grubbs catalyst and TES protection, (*E*)-enoate **6** (*E*/*Z* > 99:1) was obtained in 60% yield over two steps. Methyl ester **15** was obtained via a similar asymmetric conjugate addition of MeMgBr catalyzed by (*S*)-Tol-BINAP.[10] A further DIBAL-H reduction, followed by

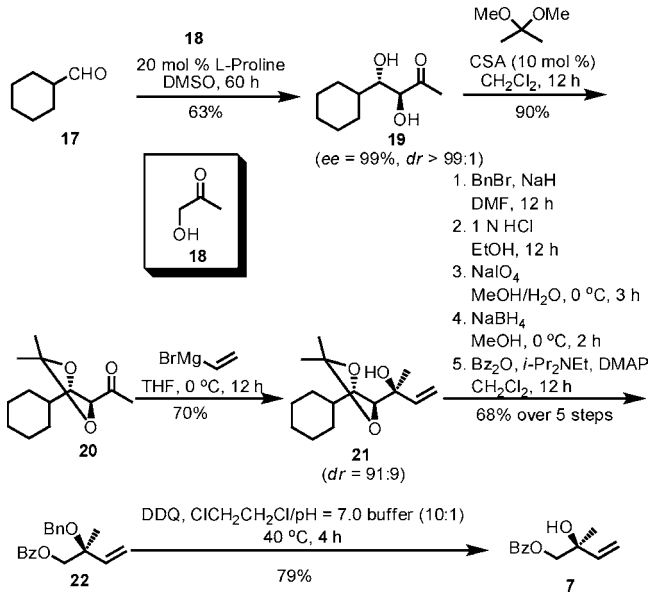
(5) Yajima, A.; Qin, Y.; Zhou, X.; Kawanishi, N.; Xiao, X.; Wang, J.; Zhang, D.; Wu, Y.; Nukada, T.; Yabuta, G.; Qi, J.; Asano, T.; Sakagami, Y. *Nat. Chem. Biol.* **2008**, *4*, 235–237.

(6) Harutyunyan, S. R.; Zhao, Z.; den Hartog, T.; Bouwmeester, K.; Minnaard, A. J.; Feringa, B. L. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 8507–8512.

(7) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 276–277.

oxidation using Dess−Martin reagent, and Wittig olefination afforded the terminal olefin **4** in 60% yields over three steps.

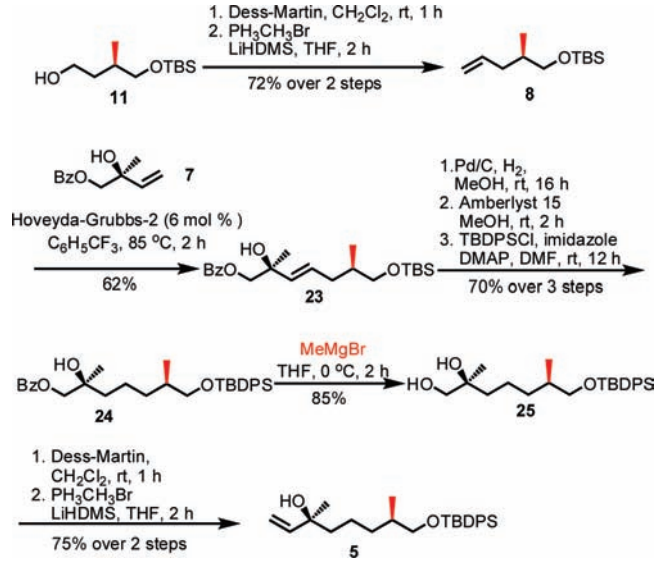
**Scheme 4.** Synthesis of **7**




As shown in Scheme 4, our synthesis of the fragment **7** utilizes an L-proline-catalyzed aldol reaction of commercially available **17** and **18** to give *anti*-diol **19** with very high enantioselectivity and moderate yield.[11] After protection of diol, tertiary **21** was obtained with 82% de by the reaction of ketone **20** with vinyl magnesium bromide.[12] After Bn protection, acetal deprotection, periodate cleavage, $NaBH_4$ reduction, and subsequent submittal to benzyl protection reaction, **24** was formed (68%, from **21**). The desired precursor **7** was obtained in 79% yield by deprotection of **24** using DDQ.[12]

The synthesis of precursor **8**, as shown in Scheme 5, was achieved from **11** by Dess−Martin oxidation followed by Wittig olefination in 72% yield. By means of cross metathesis between **7**and **8** using second-generation Hoveyda−Grubbs-2 catalyst,[9d] **23** was generated predominately in the (*E*)-configuration in 62% yield as shown in Scheme 5.[13] Hydrogenation of (*E*)-olefin **25** over Pd/C catalyst afforded the corresponding primary alcohol, which was then protected with TBDPS to give **24**. Next, the Bz group was selectively

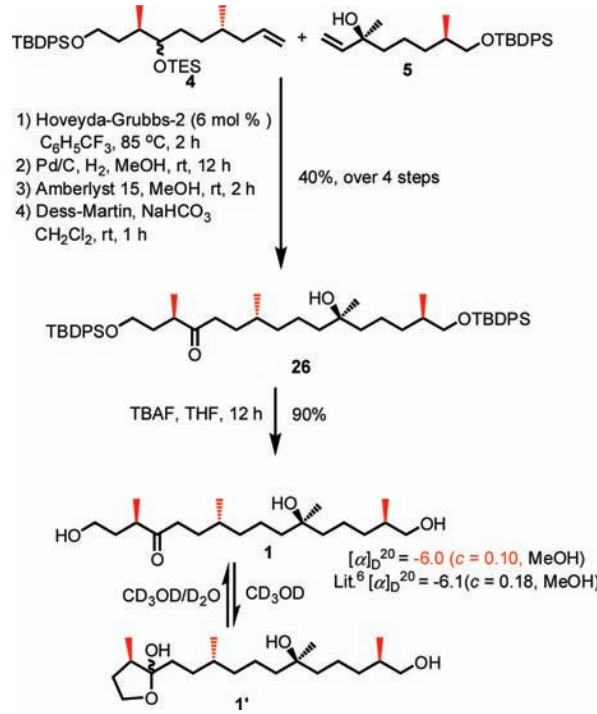
**Scheme 5.** Synthesis of **5**




deprotected and subjected to oxidation with Dess−Martin reagent, followed by Wittig olefination, leading to the terminal olefin **5** in 64% yield over three steps (Scheme 5).

Ensuing cross-metathesis of the two fragments **4** and **5** catalyzed by second-generation Hoveyda−Grubbs catalyst, hydrogenation over Pd/C, selective deprotection of TES, and Dess−Martin oxidation, **26** was obtained in 40% yield over four steps (Scheme 6). Finally, TBDPS deprotection using TBAF yields the desired (3*R*,7*R*,11*R*,15*R*)-hormone α1 (**1**) in 90% yield.[14]

**Scheme 6.** Total Synthesis of **1**




(8) (a) Wang, S.-Y.; Lum, T.-K.; Ji, S.-J.; Loh, T.-P. *Adv. Synth. Catal.* **2008**, *350*, 673–677. (b) Lum, T.-K.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2008**, *10*, 761–764.

(9) (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179. (b) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (d) Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4350–4355.

(10) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386–7387.

(11) (a) Wang, S.-Y.; Chin, Y.-J.; Loh, T.-P. *Synthesis* **2009**, 3557–3564. (b) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3674–3676.

(12) See Supporting Information. The absolute stereochemistry of **21** was determined by comparison with our previous results (ref 11).

In conclusion, we described the total synthesis of (3*R*,7*R*,11*R*,15*R*)-hormone α1 (**1**) using the asymmetric conjugate addition (CA) of MeMgBr, and cross-metathesis α1 (**1**) was constructed using the asymmetric conjugate addition (CA) of the simple Grignard reagents, of which three stereogenic centers were controlled using only one chiral ligand (*S*)-Tol-BINAP. This method could be applied to the synthesis of all the stereoisomers of hormone α1 (**1**) as well as other natural products with stereogenic centers bearing methyl groups.

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**Supporting Information Available:** Additional experimental procedures, all chromatograms, and spectral data for reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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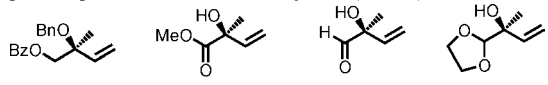
(13) The cross metathesis reaction of **8** with other functionalized tertiary alcohols such as **7a**−**7c** or **22** under the same conditions affords the corresponded products in much lower yields (< 10%).




**22** **7a** **7b** **7c**

(14) It was known that there existed an equilibrium between hormone α1 (**1**) and its hemiacetal **1′**.[5,6]