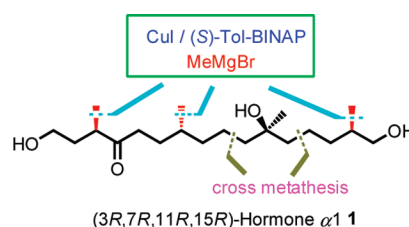


Total Synthesis of *Phytophthora* Mating
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ABSTRACT



Total synthesis of *Phytophthora* mating hormone $\alpha 1$ (**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 $\alpha 1$ (**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 $\alpha 1$ 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

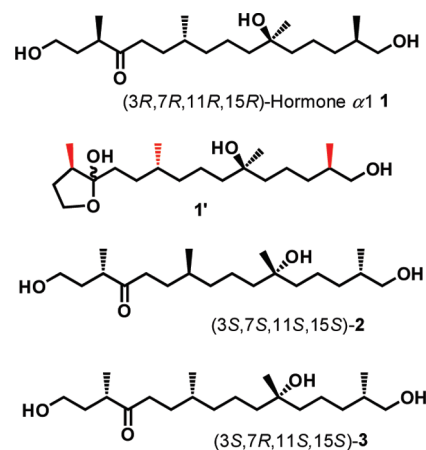


Figure 1. Structures of *Phytophthora* mating hormone $\alpha 1$ **1**, its hemiacetal **1'**, enantiomer **2**, and diastereomer **3**.

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 $\alpha 1$ (**1**).

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

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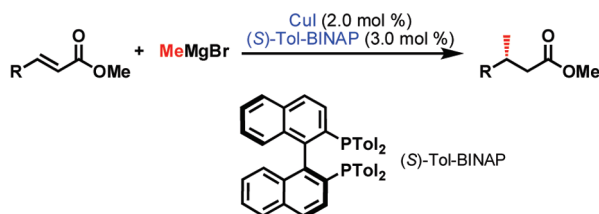
(2) Fry, W. E.; Goodwin, S. B. *Bioscience* **1997**, *47*, 363–371.

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(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.

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

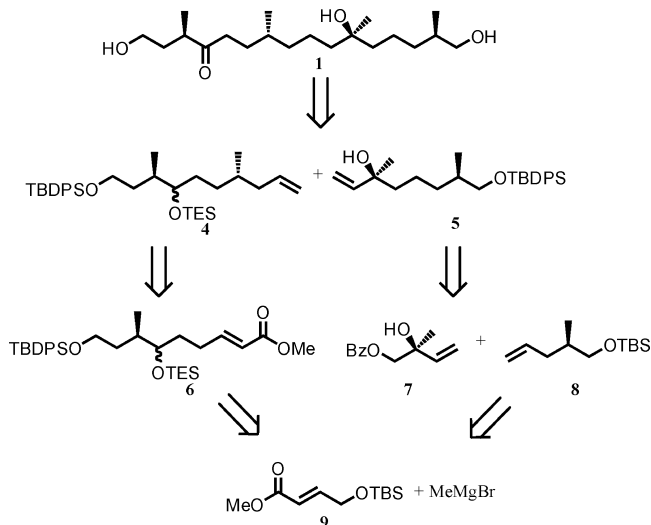
Scheme 1. General Strategy to the Synthesis of Chiral β -Methyl Esters



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

The key steps of our total synthesis of hormone α 1 (**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**.

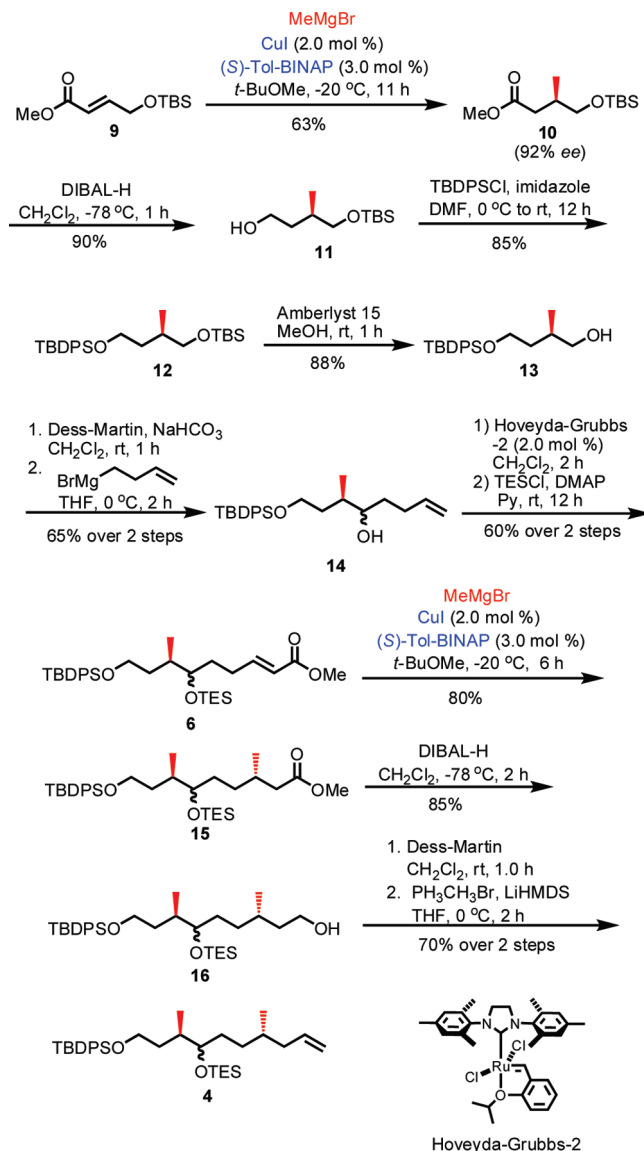
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The total synthesis of hormone α 1 (**1**) started from 1,4-conjugate addition (CA) of MeMgBr to α,β -unsaturated ester **9** catalyzed by CuI-(*S*)-Tol-BINAP (Scheme 3). The desired

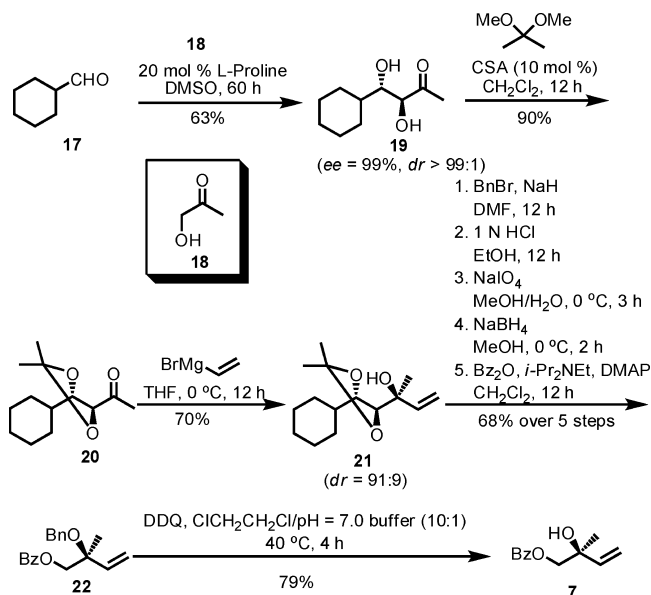
Scheme 3. Synthesis of **4**



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

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

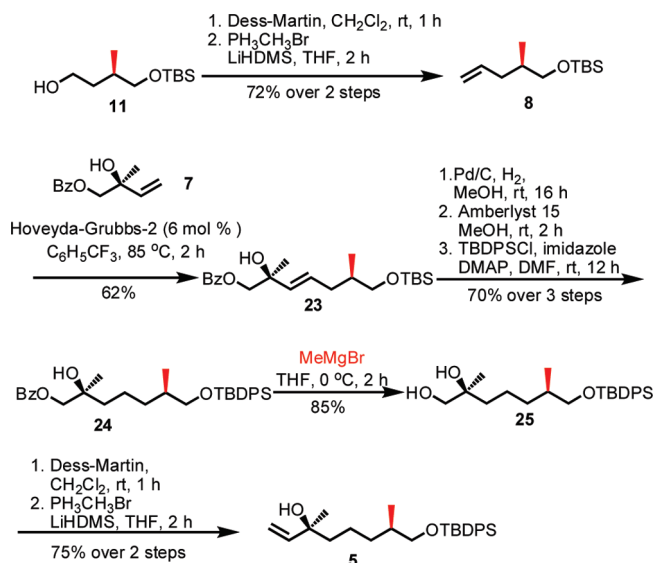
Scheme 4. Synthesis of **7**



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, NaBH₄ 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

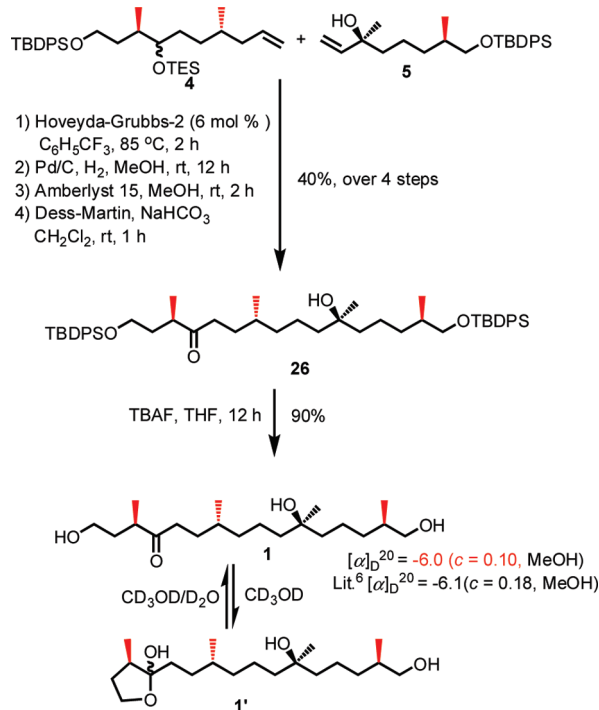
Scheme 5. Synthesis of **5**



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 **1** in 90% yield.¹⁴

Scheme 6. Total Synthesis of **1**



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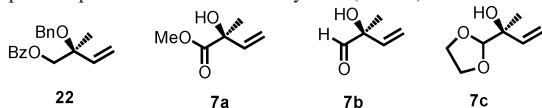
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(11) (a) Wang, S.-Y.; Chin, Y.-J.; Loh, T.-P. *Synthesis* **2009**, 3557–3564. (b) Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3674–3676.

(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 α 1 (**1**) using the asymmetric conjugate addition (CA) of MeMgBr, and cross-metathesis α 1 (**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-

(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%).



(14) It was known that there existed an equilibrium between hormone α 1 (**1**) and its hemiacetal **1'**.^{5,6}

BINAP. This method could be applied to the synthesis of all the stereoisomers of hormone α 1 (**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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