Short Stereoselective Synthesis of the *Phytophthora* Universal Mating Hormone $\alpha$1 Using Lithiation/Borylation Reactions**

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Abstract: The universal mating hormone $\alpha$1 of the virulent plant pathogen *Phytophthora* has been synthesized in 12 steps and 28% overall yield. Key C–C bond-forming steps involved the use of two lithiation/borylation reactions to couple together enantioenriched building blocks, one of which also set up the stereochemistry of the tertiary alcohol at C11. Detailed analysis showed that the diastereomeric purity of the target molecule was $> 91\%$, the highest obtained to date.

The fungus-like parasite, *Phytophthora infestans*, was responsible for the Irish potato famine in the mid-19th century, and continues to be responsible for billions of dollars worth of crop damage annually.[1] Control of this virulent plant pathogen is essential and is of increasing importance as food resources for a growing population become increasingly challenging to supply. *Phytophthora* reproduces by creating sexual spores called oospores, a process triggered by the universal hormone $\alpha$1 (1; Figure 1). Although it had been proposed as early as 1929 that sexual reproduction in *Phytophthora* was induced by a hormone-like compound,[2] it was not until 2005 that the gross structure was reported after isolation of 1.2 mg of $\alpha$1 from 1830 L of a culture broth.[3] Yajima et al. reported the first asymmetric synthesis of $\alpha$1 and concluded that the absolute configuration was (3$R$,7$R$,11$R$,15$R$) based upon oospore-inducing assays.[4] A number of total syntheses of $\alpha$1 have since been reported,[5] but in particular, the detailed and thorough analysis of all stereoisomers of 1 by Bajpai and Curran[6] is especially noteworthy.

All syntheses involve coupling of enantioenriched building blocks. This inevitably leads to diastereomers, which are essentially impossible to separate because of the remoteness of the stereogenic centers, and are therefore carried through. Based on the enantiomeric purity of the building blocks, the maximum isomeric purity of $\alpha$1 obtained in previous total syntheses ranges from 80–90%, with a 10–20% mixture of the remaining isomers. If these are divided into several diastereoisomers, they may not be readily apparent during analysis, especially as some diastereoisomers are virtually identical, thus making isomeric purity difficult to assess. Herein we report a short, highly stereoselective, and convergent synthesis of $\alpha$1 using our lithiation/borylation methodology.

Our retrosynthetic analysis of 1 involves lithiation/borylation disconnections between C3–C4 and C11–C12, thus leading to three key fragments: the secondary boronic ester 2, bis(carmamate) 3, and allylic boronic ester 4 (Scheme 1). In particular, we envisaged that 3 could be selectively lithiated at the allylic carbamate first and coupled with 4, followed by a second lithiation and coupled with 2.[7] If the fragments could be obtained in high e.r. ($\geq 99:1$), then the diastereomeric purity of the product would be determined in the lithiation/borylation reaction of the allylic carbamate, a reaction which we had found to give $\geq 98.2\%$ e.r.

Figure 1. Structure of the *Phytophthora* universal mating hormone $\alpha$1.

Supporting information for this article is available on the WWW under [http://dx.doi.org/10.1002/anie.201400714](http://dx.doi.org/10.1002/anie.201400714).
be derived from the enone 7, using Noyori’s ruthenium-catalyzed asymmetric hydrogenation,[9] which itself could be derived from citronellal. The third fragment, 4, could be derived from the allylic alcohol 8 by palladium-catalyzed borylation, and in turn 8 could be synthesized from the known aldehyde 9.

Building block 2 was prepared as shown in Scheme 2. The copper-catalyzed conjugate borylation of ethyl but-2-ynoate and subsequent asymmetric conjugate reduction gave 5 in high yield (98 %) and with excellent e.r. (99:1). Chemoselective reduction of the ester moiety in the presence of the boronic ester was achieved simply with NaBH₄. Finally, protection with TBDPS gave the desired boronic ester 2 in high yield (71 %, two steps) and high e.r. (99:1).

The synthesis of the central fragment 3 began with a Horner–Wadsworth–Emmons reaction between citronellal (99:1 e.r.) and dimethyl (2-oxopropyl)phosphonate under Masamune–Roush conditions,[10] thus giving 7 in 88 % yield (Scheme 3). Selective ozonolysis of the electron-rich trisubstituted olefin in 7 in the presence of the enone was achieved using pyridine as an additive.[11] In the presence of pyridine, the chemoselectivity of the reaction was easier to control, and since ozonides are not intermediates in the ozonolysis it is also safer. Chemoselective reduction of the aldehyde with LiAlH(O₂Bu)₃ gave the desired alcohol 10 in 74 % yield from 7 in a one-pot operation.[12] Catalytic asymmetric hydrogenation of the enone moiety in 10 with Noyori’s (S,S)-11 catalyst[8] gave the desired diol 12 in 90 % yield, 99:1 d.r., and >99:1 e.r. Finally, bis(carbamoylation) with N,N-disopropyl carbamoyl chloride gave 3 in 94 % yield.

The last of the key fragments was synthesized from the known aldehyde 9 (>99:1 e.r.), which is available in three steps from the Roche ester (Scheme 4).[13] Aldehyde 9 was treated with vinyl magnesium bromide to form the corresponding alcohol with 1:1 d.r., >99:1 e.r., and 68 % yield. After formation of the carbonate 13, palladium-catalyzed borylation with B₂(pin) gave 4 in high yield (83 %) and high e.r. (>99:1).

With the key fragments in hand, we set about their union using our lithiation/borylation methodology. Thus treatment of 3 with sBuLi/TMEDA effected chemoselective lithiation at the more acidic allylic carbamate, and addition of 4 with subsequent warming and oxidation gave the tertiary alcohol 14 in 81 % yield and 97:3 d.r. (Scheme 5).[7,14] Hydrogenation of the alkenes in 14 initially proved problematic as use of Pd/C led to a complex mixture of products, including possible epimerization at C12, silyl removal, and elimination of the tertiary alcohol. Using PtO₂ instead resulted in a much cleaner reaction, thus giving the...
corresponding tertiary alcohol in high yield (98%) and without epimerization at C12.[15]

Protection of the tertiary alcohol with TESCI gave the carbamate 15, our precursor for the second and final lithiation/borylation reaction. However, under the standard reaction conditions (Et₂O, TMEDA, sBuLi, −78°C, 5 h) we obtained a complex mixture of products. We suspected that lithiation might be the problem and so tested this part of the process by deprotonation and trapping with Me₃SnCl under a variety of conditions (Table 1). Under standard reaction conditions (Et₂O/TMEDA; entry 1), we obtained a complex mixture of products as before. The use of TBME as the solvent gave significantly improved results, thus affording approximately 94:6, thus indicating that the C7 was 99:1 (7R/7S). Stereoisomers at C11 were approximately 98:2 (11R/11S), and is consistent with the measured d.r. of 14. Thus, based on analysis of the bis-Mosher’s the overall diastereomeric purity of α1 must be > 91%, the highest measured to date.

In conclusion we have reported the shortest (12 steps, longest linear sequence), highest yielding [21.3% overall yield, (27.8% brsm)],[18] and most stereoselective synthesis (> 91% diastereomeric purity) of the α1 hormone by coupling together highly enantioenriched building blocks. Key steps involved two late-stage lithiation/borylation reactions to couple the building blocks together, thus giving high diastereocencentration (97.3) at the difficult tertiary alcohol stereocenter. Our route enables the synthesis of significant quantities of α1 (ca. 100 mg was prepared) and should thus aid the study of Phytophthora reproduction.

Keywords: asymmetric synthesis · boron · lithium · natural products · total synthesis

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Table 1: Optimization of reaction conditions for the lithiation of 15. The yield of isolated product.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Diamine</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[a]</td>
<td>Et₂O</td>
<td>TMEDA</td>
<td>0</td>
</tr>
<tr>
<td>2[a]</td>
<td>TBME</td>
<td>TMEDA</td>
<td>43</td>
</tr>
<tr>
<td>3[a]</td>
<td>TBME</td>
<td>TMEDA</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>TBME</td>
<td>(−)-sparteine</td>
<td>71</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: (8.25 equiv) carbamate 15 (1 equiv), diamine (2.1 equiv), sBuLi (2 equiv), −78°C for 5 h, then ClSnMe₃ (2.5 equiv).

Scheme 6. Coupling of the boronic ester 2 with the carbamate 12, and completion of the synthesis. DMP = Dess−Martin periodinane, TBAF = tetra-n-butylammonium fluoride.


