Natural Product Synthesis

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Short Stereoselective Synthesis of the *Phytophthora* Universal Mating Hormone α1 Using Lithiation/Borylation Reactions**

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Abstract: *The universal mating hormone α1 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 α1 (**1**; Figure 1). Although it had been

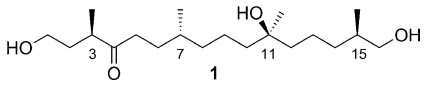
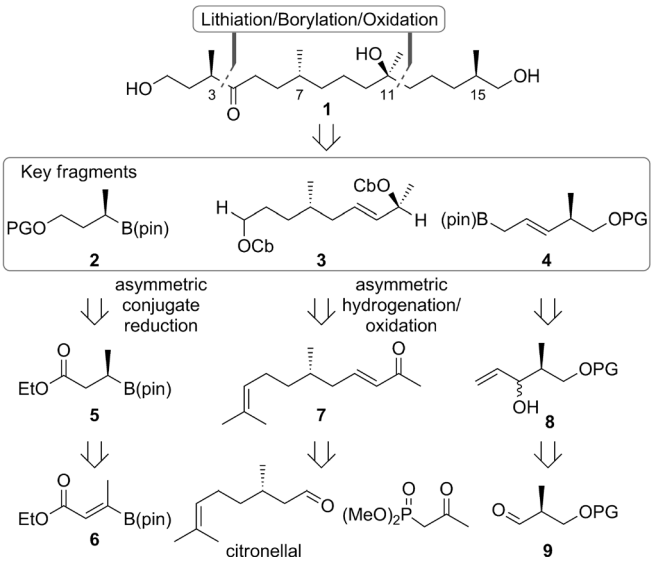


Figure 1. Structure of the *Phytophthora* universal mating hormone α1.

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 α1 from 1830 L of a culture broth.[3] Yajima et al. reported the first asymmetric synthesis of a stereoisomer library of α1 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 **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 α1 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 α1 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(carbamate) **3**, and allylic boronic ester **4** (Scheme 1). In



Scheme 1. Retrosynthetic analysis of **1**. PG = protecting group, pin = pinacolato, Cb = *N*,*N*-diisopropyl carbamoyl.

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. (≥ 99:1), then the diasteromeric purity of the product would be determined in the lithiation/borylation reaction of the allylic carbamate, a reaction which we had found to give ≥ 98:2 e.r.

Fragment **2** could be derived from the known β-boronic ester **5** and vinyl boronic ester **6**. We anticipated that **3** could

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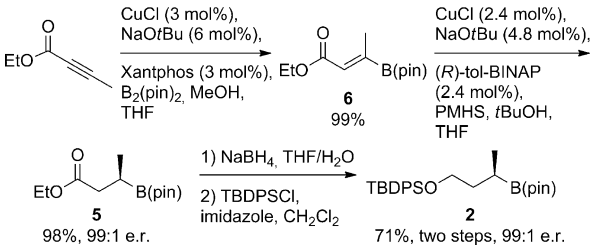
be derived from the enone **7**, using Noyori's ruthenium-catalyzed asymmetric hydrogenation,[8] which itself could be derived from citronellal. The third fragment, **4**, could be derived from the allylic alcohol **8** by palladium-catalyzed borylation, and in turn **8** could be synthesized from the known aldehyde **9**.

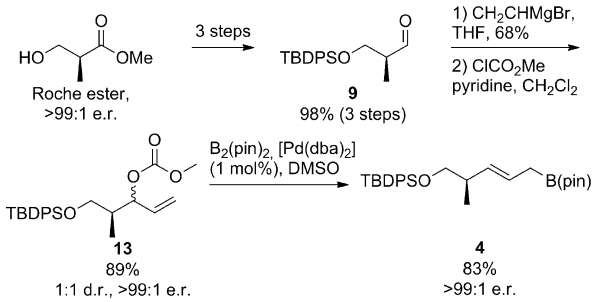
Building block **2** was prepared as shown in Scheme 2. The copper-catalyzed conjugate borylation of ethyl but-2-ynoate and subsequent asymmetric conjugate reduction gave **5** in high yield (98%) and with excellent e.r. (99:1).[9] Chemoselective reduction of the ester moiety in the presence of the boronic ester was achieved simply with $NaBH_4$. Finally, protection with TBDPS gave the desired boronic ester **2** in high yield (71%, two steps) and high e.r. (99:1).



Scheme 2. Synthesis of fragment **2**. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, PMHS = polymethylhydrosiloxane, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

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 $LiAlH(OtBu)_3$ 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*-diisopropyl carbamoyl chloride gave **3** in 94% yield.

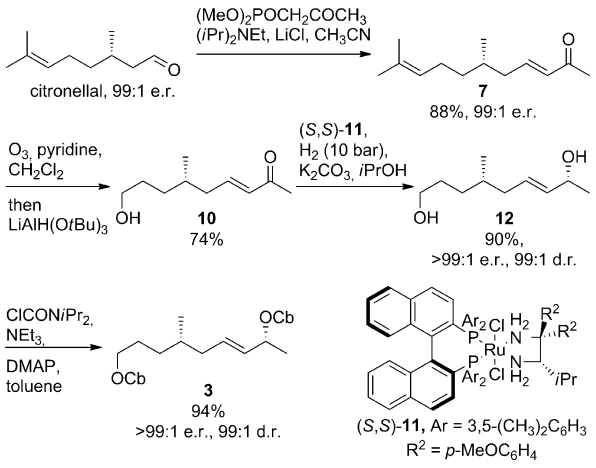
The last of the key fragments was synthesized from the known aldehyde **9** (> 99:1 e.r.), which is available in three steps from the Roche ester (Scheme 4).[13] Aldehyde **9** was treated with vinyl magnesium bromide to form the corresponding alcohol with 1:1 d.r., > 99:1 e.r., and 68% yield. After formation of the carbonate **13**, palladium-catalyzed borylation with $B_2(pin)_2$ gave **4** in high yield (83%) and high e.r. (> 99:1).



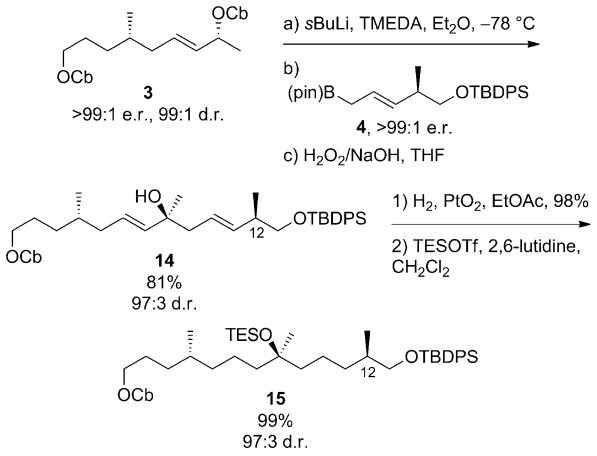
Scheme 4. Synthesis of the boronic ester **4** from the Roche ester. dba = dibenzylideneacetone, DMSO = dimethylsulfoxide.

With the key fragments in hand, we set about their union using our lithiation/borylation methodology. Thus treatment of **3** with *s*BuLi/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 PtO_2 instead resulted in a much cleaner reaction, thus giving the



Scheme 3. Synthesis of the bis(carbamate) **3** from citronellal. DMAP = 4-(*N*,*N*-dimethyl)pyridine.

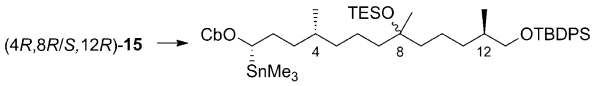


Scheme 5. Union of **4** and **3**. TES = triethylsilyl, Tf = trifluoromethanesulfonyl.

corresponding tertiary alcohol in high yield (98%) and without epimerization at C12.[15]

Protection of the tertiary alcohol with TESCl gave the carbamate **15**, our precursor for the second and final lithiation/borylation reaction. However, under the standard reaction conditions (Et_2O, TMEDA, *s*BuLi, −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 Me_3SnCl under a variety of conditions (Table 1). Under standard reaction conditions (Et_2O/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

Table 1: Optimization of reaction conditions for the lithiation of **15**.[a]



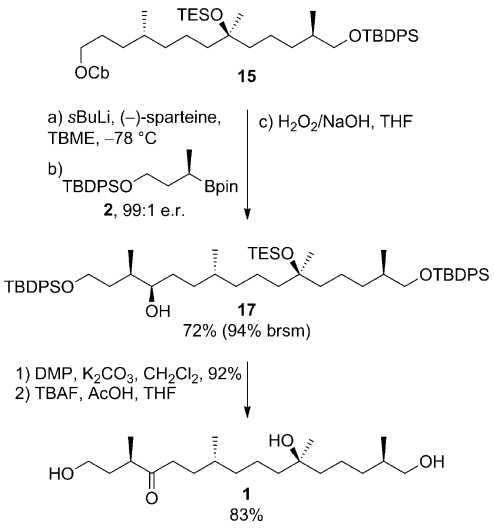
Entry	Solvent	Diamine	Yield [%][b]	
			16	**15**
1[c]	Et_2O	TMEDA	0	18
2[c]	TBME	TMEDA	43	0
3[c]	TBME	TMCDA	40	0
4	TBME	(−)-sparteine	71	22

[a] Reaction conditions: (8*R*/*S*)-carbamate **15** (1 equiv), diamine (2.1 equiv), *s*BuLi (2 equiv), −78 °C for 5 h, then $ClSnMe_3$ (2.5 equiv). [b] Yield of isolated product. [c] Reactions contained numerous unidentified side products. TBME = *tert*-butylmethyl ether, TMCDA = (*rac*,*trans*)-*N*,*N*,*N*′,*N*′-tetramethylcyclohexane-1,2-diamine, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

40% of the stannane **16** (entry 2). Alternative diamines were then explored as they can have a major impact on the outcome of lithiation reactions. Whilst TMCDA gave similar results, use of the more hindered (−)-sparteine gave **16** in high yield (71%) together with the recovered starting material **15** (22%; entries 3 and 4).[16,17]

By using these reaction conditions in the lithiation/borylation reaction with **2** and subsequent oxidation, the desired secondary alcohol was obtained in 72% yield, together with the recovered carbamate **15** in 24% (94% brsm, Scheme 6). Oxidation of the secondary alcohol with Dess–Martin periodinane gave the known ketone,[5a] and subsequent deprotection with TBAF in AcOH/THF, as described by Yajima et al.,[4] gave α1 in high yield (83%). Its characterization data was identical to that of the reported data in every respect.

Based on the enantiomeric purity of the building blocks the maximum isomeric purity of α1 was calculated to be 96:4, which is considerably greater than any previous synthesis. To measure the isomeric purity, the bis-Mosher's ester of α1 was prepared and analyzed according to Curran's stereoisomer method.[6] The product was determined to be 95:5 at C3 (3*R*/3*S*), thus indicating that a small degree of epimerization at the labile C3 center had occurred during deprotection, and 99:1 at C15 (15*R*/15*S*). The *anti*/*syn* (C3/C7) ratio was



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.

approximately 94:6, thus indicating that the C7 was 99:1 (7*R*/7*S*). Stereoisomers at C11 were approximately 98:2 (11*R*/11*S*), 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 diastereocontrol (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.

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[16] TES protection of the tertiary alcohol in **15** was important for high yields. Attempted double lithiation of the free tertiary alcohol (**15** minus TES) with excess *s*BuLi under the optimized reaction conditions (Table 1, entry 4) gave 15% of the intended stannane and 60% of the recovered starting material.

[17] We considered the use of hindered achiral diamines such as *N*,*N*-di-*n*-butyl bispidine as it has similar reactivity to (−)-sparteine with regard to lithiation efficiency. See: M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun.* **2006**, 2607. However, *N*,*N*-di-*n*-butyl bispidine is not as available as (−)-sparteine.

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