OPEN ACCESS

University of BRISTOL

Peer reviewed version

Link to published version (if available):
10.1002/anie.201400714

Link to publication record in Explore Bristol Research
PDF-document

University of Bristol - Explore Bristol Research

General rights

Short Stereoselective Synthesis of the *Phytophthora* Universal Mating Hormone Alpha 1 using Lithiation/Borylation Reactions**

Alexander P. Pulis,[+] Philipp Fackler[+] and Varinder K. Aggarwal

Abstract: Alpha 1, the universal mating hormone 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 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 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 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 culture broth.[3] Yajima 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 Curran[6] is especially noteworthy.

All syntheses involve coupling of enantioenriched building blocks. This inevitably leads to diastereomers, which are essentially impossible to separate due to the remoteness of the stereogenic centres and so are 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 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, making isomeric purity difficult to assess. In this paper 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, leading to three key fragments: secondary boronic ester (BE) **2**, bis-carbamate **3**, and allylic BE **4** (Scheme 1). In particular, we envisaged that the bis-**3** could be selectively lithiated at the allylic carbamate first and coupled with allylic BE **4**, followed by a second lithiation and coupled with secondary BE **2**.[7] If the fragments could be obtained in high *er* (≥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 *er*.

Fragment **2** could be derived from the known β-BE **5** and vinyl BE **6**. We anticipated that bis-carbamate **3** could be derived from enone **7** using Noyori's Ru-catalyzed asymmetric hydrogenation,[8] which itself could be derived from citronellal. The third fragment, allylic BE **4**, could be derived from allylic alcohol **8** via Pd catalysed borylation, which in turn could be synthesised from the known aldehyde **9**.

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

The synthesis of the central fragment **3** began with Horner-Wadsworth-Emmons reaction between citronellal (99:1 *er*) and dimethyl (2-oxopropyl)phosphonate under Masamune-Roush conditions[10] giving enone **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 safer too. Chemoselective reduction of the aldehyde with $LiAlH(OtBu)_3$ gave the desired alcohol **10** in 74% yield from enone **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 and 99:1 *dr* and >99:1 *er*. Finally, bis-carbamoylation with *N,N*-diisopropyl carbamoyl chloride gave the desired bis-carbamate **3** in 94% yield.

The last of the key fragments was synthesised from known aldehyde **9** (>99:1 *er*), available in 3 steps from the Roche ester (Scheme 4).[13] Aldehyde **9** was treated with vinyl magnesium bromide to form the corresponding alcohol in 1:1 *dr*, >99:1 *er* and 68% yield. Following formation of carbonate **13**, palladium catalyzed borylation with $B_2(pin)_2$ gave the desired allylic BE **4** in high yield (83%) and *er* (>99:1).

With the key fragments in hand, we set about their union using our lithiation/borylation methodology. Thus treatment of bis-carbamate **3** with *s*BuLi/TMEDA effected chemoselective lithiation

[∗]   Dr. A. P. Pulis, Dr. P. Fackler, Prof. V. K. Aggarwal
      School of Chemistry, University of Bristol
      Cantock's Close, Bristol, BS8 1TS
      E-mail: v.aggarwal@bristol.ac.uk
      Homepage:
      http://www.bris.ac.uk/chemistry/research/organic/aggarwal-group

[†]   These authors contributed equally to this work.

at the more acidic allylic carbamate and addition of the allylic BE **4** followed by warming and oxidation gave tertiary alcohol **14** in 81% yield and 97:3 *dr* (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 epimerisation at C12, silyl deprotection and elimination of the tertiary alcohol. Using PtO_2 instead resulted in a much cleaner reaction giving the corresponding tertiary alcohol in high yield (98%) and without epimerization at C12.[15]

Protection of the tertiary alcohol with TESCl gave carbamate **15**, our precursor for the second and final lithiation/borylation reaction. However, under the standard condition (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 conditions [Et_2O/TMEDA (Entry 1)], we obtained a complex mixture of products as before. The use of TBME as solvent gave significantly improved results affording 40% of 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 the stannane **16** in high yield (71%) together with recovered starting material **15** (22%) (Entry 3 and 4).[16,17]

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

Entry	Solvent	Diamine	Yield of **16** / %[b]	Yield of **15** / %[b]
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]Conditions: (8*R/S*)-carbamate **15** (1 eq), diamine (2.1 eq), *s*BuLi (2 eq), −78 °C for 5 h, then $ClSnMe_3$ (2.5 eq). [b]Isolated yield. [c]Reactions contained numerous unidentified side products. TMCDA = (*rac,trans*)-N,N,N',N'-tetramethylcyclohexane-1,2-diamine.

Using these conditions in the lithiation/borylation reaction with secondary BE **2** followed by oxidation gave the desired secondary alcohol in 72% yield together with 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[4] gave α1 in high yield (83%). Its characterization data was identical with 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, considerably greater than any previous synthesis. In order to measure the isomeric purity, the bis-Moshers ester of α1 was prepared and analysed according to Curran's stereoisomer method.[6] The product was determined to be 95:5 at C3 (3*R*:3*S*) 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 approximately 94:6 indicating that the C7 was 99:1 (7*R*:7*S*). Stereoisomers at C11 was approximately 98:2 (11R:11S), consistent with the measured dr of intermediate **14**. Thus, based on analysis of the bis-Mosher's ester 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, giving high diastereocontrol (97:3) at the difficult tertiary alcohol stereocentre. Our route enables the synthesis of significant quantities of α1 (~100 mg was prepared) which should aid the study of *Phytophthora* reproduction.

[1] a) B. J. Haas, *et al*, *Nature* **2009**, *461*, 393; M. Nowicki, M. R. Foolad, M. Nowakowska, E. U. Kozik, *Plant Disease* **2012**, *96*, 4.

[2] S. F. Ashby, *Trans. Br. Mycol. Soc.* **1929**, *14*, 18.

[3] a) J. Qi, T. Asano, M. Jinno, K. Matsui, K. Atsumi, Y. Sakagami, M. Ojika, *Science* **2005**, *309*, 1828; b) M. Ojika, J. Qi, Y. Kito, Y. Sakagami, *Tetrahedron: Asymmetry* **2007**, *18*, 1763

[4] A. Yajima, Y. Qin, X. Zhou, N. Kawanishi, X. Xiao, J. Wang, D. Zhang, Y. Wu, T. Nukada, G. Yabuta, J. Qi, T. Asano, Y. Sakagami, *Nat. Chem. Biol.* **2008**, *4*, 235.

[5] For syntheses where all stereocenters were controlled, see: a) S. R. Harutyunyan, Z. Zhao, T. d. Hartog, K. Bouwmeester, A. J. Minnaard, B. L. Feringa, F. Govers, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 8507; b) S.-Y. Wang, P. Song, L.-Y. Chan, T.-P. Loh, *Org. Lett.* **2010**, *12*, 5166; and references 4 and 6. For other syntheses where one or more stereocenters was not controlled, see: c) A. Yajima, N. Kawanishi, J. Qi, T. Asano, Y. Sakagami, T. Nukadaa, G. Yabutaa, *Tetrahedron Lett.* **2007**, *48*, 4601; d) R. Bajpai, F. Yang, D. P. Curran, *Tetrahedron Lett.* **2007**, *48*, 7965; e) A. Yajima, K. Toda, S. D. Molli, M. Ojika, T. Nukada, *Tetrahedron* **2011**, *67*, 8887.

[6] R. Bajpai, D. P. Curran, *J. Am. Chem. Soc.* **2011**, *133*, 20435.

[7] Primary alkyl carbamates are usually lithiated with *s*BuLi/TMEDA in Et_2O at −78 °C within 5 h. Secondary allylic carbamates generally undergo complete lithiation within a few minutes under the same conditions. For lithiation/borylation of alkyl carbamates, see: a) J. L. Stymiest, G. Dutheuil, A. Mahmood, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2007**, *46*, 7491; *Angew. Chem.* **2007**, *119*, 7475. For lithiation/borylation of secondary allylic carbamates, see: b) A. P. Pulis, V. K. Aggarwal, *J. Am. Chem. Soc.* **2012**, *134*, 7570.

[8] T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 13529.

[9] H. −Y. Jung, X. Feng, H. Kim, J. Yun, *Tetrahedron* **2012**, *68*, 3444.

[10] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.

[11] R. Willand-Charnley, T. J. Fisher, B. M. Johnson, P. H. Dussault, *Org. Lett.* **2012**, *14*, 2242.

[12] Using catalyst **11**, reduction of the of the aldehyde-enone obtained after ozonolysis (without the LiAlH(O*t*Bu)₃ reduction step) was unsuccessful and gave a mixture of products.

[13] J. Cossy, D. Bauer, V. Bellosta, *Tetrahedron* **2002**, *58*, 5909.

[14] These results suggest that coordination of *s*BuLi to the carbonyl of the primary alkyl carbamate is reversible, allowing for complete lithiation at the α-oxygen allylic site. Reversibility in pre-lithiation complexes of alkyl carbamates has been noted by others, see M. J. McGrath, P. O'Brien, *Synthesis* **2006**, 13, 2233.

[15] Epimerization in similar Pd/C or Pd(OH)₂/C hydrogenations have been reported: a) T. Nakai, A. Yajima, K. Akasaka, T. Kaihoko, M. Ohtaki, H. Nukuda, H. Ohrui, G. Yabuta, *Biosci. Biotechnol. Biochem.* **2005**, *69*, 2401; b) J. Buter, E. A.-H. Yeh, O. W. Budavich, K. Damodaran, A. J. Minnaard, D. P. Curran, *J. Org. Chem.* **2013**, *78*,

4913; c) reference 4. The use of PtO$_2$ or Pt avoided epimerization: see reference 15a and 15b.

[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 optimised conditions from Table 1, Entry 4 gave 15% of the intended stannane and 60% 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.

[18] Previous stereoselective syntheses range from 17-21 steps and 2-7% overall yield.

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

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

Scheme 2. Synthesis of fragment **2**. PMHS = polymethylhydrosiloxane, TBDPS = *tert*-butyldiphenylsilyl.

Scheme 3. Synthesis of bis-carbamate **3** from citronellal.

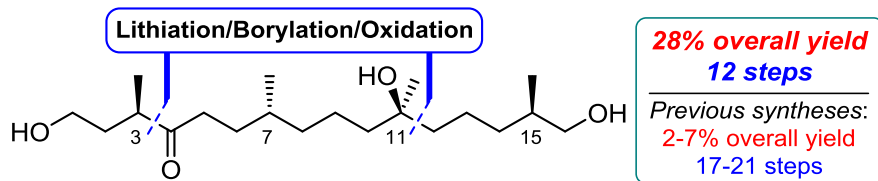**Scheme 4.** Synthesis of boronic ester **4** from the Roche ester.

Scheme 5. Union of allylic boronic ester **4** and biscarbamate **3**. TES = triethyl silyl.

Scheme 6. Coupling of boronic ester **2** with carbamate **12** and completion of the synthesis.

Natural Products

Alexander P. Pulis, Philipp Fackler and Varinder K. Aggarwal * _____ **Page – Page**

Short Stereoselective Synthesis of the Phytophthora Universal Mating Hormone Alpha 1 using Lithiation/Borylation Reactions

Lithiation/Borylation/Oxidation

28% overall yield
12 steps
Previous syntheses:
2-7% overall yield
17-21 steps

Alpha 1, the universal mating hormone 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 at C11. Detailed analysis showed that the diastereomeric purity of the target molecule was >91%, the highest obtained to date.