A General Method for Convergent Synthesis of Polycyclic Ethers Based on Suzuki Cross-Coupling: Concise Synthesis of the ABCD Ring System of Ciguatoxin

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ABSTRACT



A general method for convergent assembly of polyether structure has been developed based on palladium(0)-mediated Suzuki cross-coupling reaction of alkylboranes with cyclic ketene acetal phosphates. The present method allowed for coupling of medium-sized ether rings and thus a concise synthesis of the ABCD ring system of ciguatoxins has been achieved.

Marine polycyclic ethers, such as brevetoxins, ciguatoxins, and maitotoxin, present formidable and challenging synthetic targets due to their structural complexity and exceptionally potent biological activities.¹ One of the most critical issues in the synthesis of these large natural products is the development of synthetic methods for convergent coupling of polyether fragments. Despite recent advances in the synthesis of medium-sized cyclic ethers,² only a few methods for the convergent assembly of polyether structure have been reported to date.³ In connection with the synthetic studies on ciguatoxins,^{4,5} we have recently developed a new strategy

for convergent synthesis of polyether frameworks based on palladium(0)-catalyzed Suzuki cross-coupling of alkylboranes with cyclic ketene acetal triflates.^{6,7} Although this method has represented a powerful tool for the efficient construction of trans-fused polytetrahydropyran ring systems via coupling of six-membered rings, seven-membered ketene acetal triflates could not be utilized as the substrates in this coupling reaction due to their instability under the aqueous basic

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conditions. Herein, we report the first Suzuki cross-coupling of alkylboranes with cyclic ketene acetal phosphates, superior substrates to the corresponding triflates with respect to their stability and handling.^{8,9} The present method allowed for a general approach to convergent synthesis of polycyclic ethers containing medium-sized rings, and a concise synthesis of the ABCD ring system of ciguatoxin analogues (CTX3C **1** and 51-hydroxyCTX3C **2**, Figure 1)^{10,11} has been achieved accordingly.



Figure 1. Structure of CTX3C (1) and 51-HydroxyCTX3C (2).

We chose to examine the cross-coupling of the alkylborane generated in situ via the hydroboration of *exo*-olefin 3^{12} with cyclic ketene acetal phosphate $4a^{13}$ as a model system to establish the reaction conditions (eq 1, Table 1). Hydrobo-

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(9) Very recently, nickel(0)- and palladium(0)-catalyzed Suzuki crosscoupling reactions of arylboronic acids with enol phosphates have been reported, see (a) Huffman, M. A.; Yasuda, N. *Synlett* **1999**, 471. (b) Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, 40, 3321. **Table 1.** Suzuki Cross-Coupling of Alkylborane Derived from *exo*-Olefin **3** with Cyclic Ketene Acetal Phosphates $(eq 1)^a$





^{*a*} exo-Olefin **3** was hydroborated with 9-BBN (2.6 equiv, THF, r.t. \rightarrow 60 °C) and then treated in situ with aqueous 1 M NaHCO₃ (3 equiv), Pd(PPh₃)₄ (0.1 equiv), and cyclic ketene acetal phosphate **4** (2 equiv) in DMF at 50 °C for 20 h. ^{*b*}Cyclic ketene acetal phosphates were prepared from the corresponding lactones [KHMDS, THF-HMPA, (PhO)₂P(O)Cl, -78 °C] following the procedure of Nicolaou et al.^{8a} ^cThe use of 1 equiv of **4a**.

ration of **3** with 9-BBN (2.6 equiv, THF, r.t. to 60 °C) provided the corresponding alkylborane, which was in situ coupled with 1 equiv of **4a** under conventional Suzuki conditions [aqueous K_3PO_4 , Pd(PPh₃)₄, DMF] to yield the desired coupling product **5a** albeit in moderate yield (46–

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⁽¹²⁾ Synthetic scheme for compound $\mathbf{3}$ is included as Supporting Information.

⁽¹³⁾ The ketene acetal phosphates were prepared from the corresponding lactones following the procedure of Nicolaou et al., see ref 8.

Scheme 1. Synthesis of the ABCD Ring System of CTX3C^a



^{*a*} Reagents and conditions: (a) Thexylborane, THF, $-20 \rightarrow 0$ °C, then H₂O₂, NaOH; (b) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C \rightarrow r.t.; (c) TsOH, MeOH–CH₂Cl₂ (4:1), r.t. \rightarrow 55 °C; (d) SO₃·Pyr, Et₃N, DMSO, CH₂Cl₂, 0 °C \rightarrow r.t.; (e) Ph₃P⁺CH₃Br⁻, NaHMDS, THF, 0 °C; (f) Et₃SiH, BF₃·OEt₂, CH₂Cl₂–CH₃CN (5:3), r.t.; (g) I₂, CH₂Cl₂, 0 °C \rightarrow r.t.; (h) Zn, AcOH, Et₂O–MeOH, r.t.; (i) NaHMDS, allyl bromide, DMF, 0 °C \rightarrow r.t.; (j) RuCl₂(=CHPh)(PCy₃)₂, CH₂Cl₂, r.t.

56%). Presumably, hydrolysis of **4a** would occur competitively under these conditions due to the slow rate of oxidative addition of less reactive **4a** to the palladium(0) complex. The yield of **5a** was improved by carrying out the reaction with aqueous NaHCO₃ as a milder base instead of K₃PO₄ (Table 1, entry 1). Finally, the best result was obtained when excess **4a** (2 equiv) was employed, giving **5a** in nearly quantitative yield (entry 3). Other phosphine-free palladium catalysts such as Pd₂(dba)₃•CHCl₃ proved ineffective, which is consistent with the results of cross-coupling of phenylboronic acid with an enol phosphate.^{9a}

It is noteworthy that this coupling reaction can be applied to not only six-membered ketene acetal phosphates but also medium-sized rings (Table 1, entries 4–8), including eightmembered ring where the corresponding triflates are known to be difficult to prepare.¹⁴ Since the seven-membered ketene acetal triflate decomposed even under these mild conditions,¹⁵ use of the phosphate leaving group is essential for this coupling reaction. The present method therefore appears to be quite general and efficient for synthesis of polycyclic ethers containing medium-sized rings.

The usefulness of the described method has been demonstrated in the concise synthesis of the ABCD ring system of CTX3C series (1, 2) (Scheme 1). Hydroboration of **5c** with thexylborane proceeded regio- and stereoselectively to give, after oxidative workup, alcohol **6** in 73% yield (86% based on recovered **5c**). Oxidation under Swern conditions followed by acidic treatment in MeOH effected removal of the TBS and MOM groups and concomitant acetal formation giving hydroxy methyl acetal **7** in 82% overall yield. Further oxidation to the corresponding aldehyde followed by Wittig reaction provided terminal olefin **8** in 79% yield for the two steps. Reduction of **8** with Et₃SiH–BF₃•OEt₂ proceeded smoothly to give tricyclic ether **9** as a single stereoisomer in 86% yield. Regioselective debenzylation of **9** was carried out according to the method of Cipolla et al.¹⁶ to provide alcohol **10**, which was allylated giving bisolefin **11** in 65% overall yield. Finally, ring-closing metathesis of **11** by using Grubbs' catalyst [RuCl₂(=CHPh)(PCy₃)₂]¹⁷ furnished the desired ABCD ring system **12**¹⁸ in quantitative yield. Thus, a concise and rapid synthesis of **12** was achieved in 10 steps and 30% overall yield from **3**.

In conclusion, we have demonstrated Suzuki crosscoupling of alkylboranes with cyclic ketene acetal phosphates to be a powerful tool for the construction of polycyclic ethers containing medium-sized rings. The present methodology is thus believed to allow a general approach to convergent syntheses of polyether marine toxins. Further studies toward the total synthesis of ciguatoxins and their simplified analogues based on the present strategy are currently underway and will be reported in due course.

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Supporting Information Available: Synthetic schemes for compounds **3** and **4a–e**, typical experimental procedures for synthesis of **4** and Suzuki cross-coupling reaction, spectroscopic data for compounds **5a–f**, experimental procedures and spectroscopic data for compounds **6-12**, and ¹H and ¹³C NMR spectra for compound **12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁵⁾ Reaction of the seven-membered ketene acetal triflate corresponding to **4c** [aqueous 1 M NaHCO₃ (3 equiv), Pd₂(dba)₃•CHCl₃ (0.05 equiv), Ph₃-As (0.4 equiv), DMF, r.t. 20 h] gave **5c** in only 29% yield.

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