ORGANIC LETTERS

1999
Vol. 1, No. 7
1075−1077

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

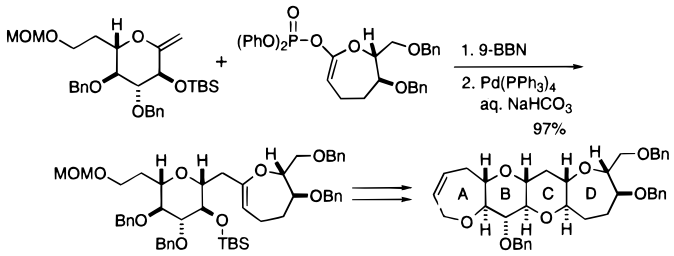
Makoto Sasaki,* Haruhiko Fuwa, Makoto Ishikawa, and Kazuo Tachibana

Department of Chemistry, School of Science, The University of Tokyo, and CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

msasaki@chem.s.u-tokyo.ac.jp.

Received July 28, 1999

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

(1) For recent reviews on ciguatoxins and related marine toxins, see (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.

(2) For recent reviews on polyether synthesis, see (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953. (b) Mori, Y. *Chem. Eur. J.* **1997**, *3*, 849.

(3) (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321. (b) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (c) Oishi, T.; Nagumo, Y.; Hirama, M. *Synlett* **1997**, 980. (d) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (e) Nicolaou, K. C.; Gunzner, J. L.; Shi, G.-q.; Agrios, K. A.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 646. (f) Very recently, the ABCDE ring framework of ciguatoxin has been prepared using alkylation-ring-closing metathesis approach; Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M.; *Chem. Commun.* **1999**, 1063.

10.1021/ol990885n CCC: $18.00
Published on Web 09/14/1999

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.

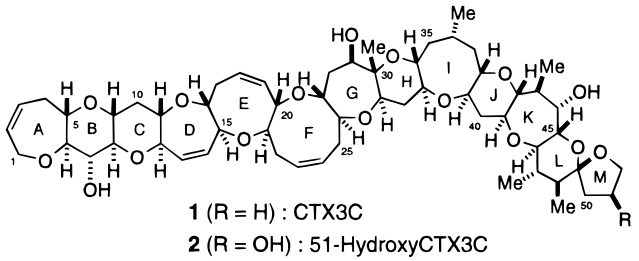
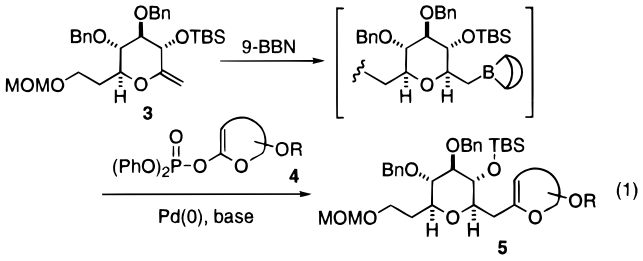
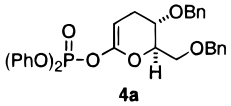
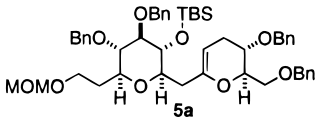
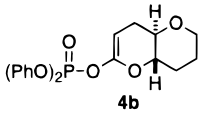
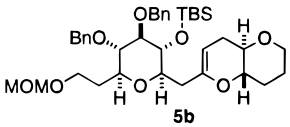
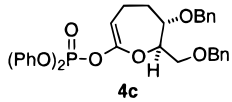
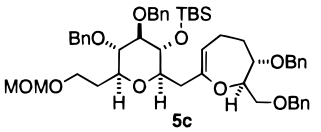
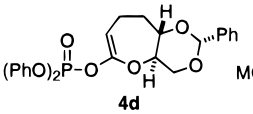
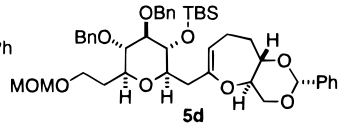
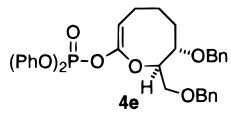
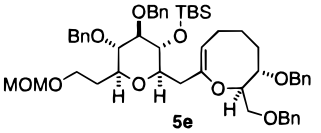
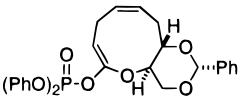
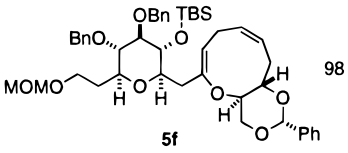


Figure 1. Structure of CTX3C (**1**) and 51-HydroxyCTX3C (**2**).

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). Hydroboration 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, $Pd(PPh_3)_4$, DMF] to yield the desired coupling product **5a** albeit in moderate yield (46−

Table 1. Suzuki Cross-Coupling of Alkylborane Derived from *exo*-Olefin **3** with Cyclic Ketene Acetal Phosphates (eq 1)[a]



Entry	Phosphate[b]	Product	%Yield
1[c]			72
2[d]			84
3	**4a**	**5a**	98
4	 **4b**	 **5b**	87
5	 **4c**	 **5c**	97
6	 **4d**	 **5d**	94
7	 **4e**	 **5e**	96
8	 **4f**[8a]	 **5f**	98

[a] *exo*-Olefin **3** was hydroborated with 9-BBN (2.6 equiv, THF, r.t. → 60 °C) and then treated in situ with aqueous 1 M $NaHCO_3$ (3 equiv), $Pd(PPh_3)_4$ (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] [c]The use of 1 equiv of **4a**. [d]The use of 1.4 equiv of **4a**.

(4) (a) Sasaki, M.; Hasegawa, A.; Tachibana, K. *Tetrahedron Lett.* **1993**, *34*, 8489. (b) Sasaki, M.; Inoue, M.; Tachibana, K. *J. Org. Chem.* **1994**, *59*, 715. (c) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **1997**, *38*, 1611. (d) Inoue, M.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 965. (e) Sasaki, M.; Inoue, M.; Noguchi, T.; Takeichi, A.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 2783. (f) Sasaki, M.; Noguchi, T.; Tachibana, K. *Tetrahedron Lett.* **1999**, *40*, 1337. (g) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949.

(5) For recent synthetic studies from other groups, see (a) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1996**, *52*, 12091. (b) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett* **1996**, 1165. (c) Alvarez, E.; Delgado, M.; Díaz, M. T.; Hanxing, L.; Pérez, R.; Martín, J. D. *Tetrahedron Lett.* **1996**, *37*, 2865. (d) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* **1996**, 473. (e) Atsuta, H.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 307. (f) Oishi, T.; Maeda, K.; Hirama, M. *Chem. Commun.* **1997**, 1289. (g) Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* **1997**, *53*, 3057. (h) Oishi, T.; Shoji, M.; Kumahara, N.; Hirama, M. *Chem. Lett.* **1997**, 845. (i) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1997**, *38*, 8053. (j) Ami, E.; Kishimoto, H.; Ohrui, H.; Meguro, H. *Biosci. Biotech. Biochem.* **1997**, *61*, 2019. (k) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1. (l) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* **1998**, *54*, 21. (m) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (n) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* **1998**, 2665. (o) Hosokawa, S.; Isobe, M. *J. Org. Chem.* **1999**, *64*, 37. (p) Saeeng, R.; Isobe, M. *Tetrahedron Lett.* **1999**, *40*, 1911. (q) Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405 and references therein.

(6) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027.

(7) For a review on Suzuki cross-coupling reaction, see Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(8) Cyclic ketene acetal phosphates were successfully used for palladium(0)-catalyzed Stille coupling, leading to the total synthesis of brevetoxin A, see (a) Nicolaou, K. C.; Shi, G. Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467. (b) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-q.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618.

(9) Very recently, nickel(0)- and palladium(0)-catalyzed Suzuki cross-coupling 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.

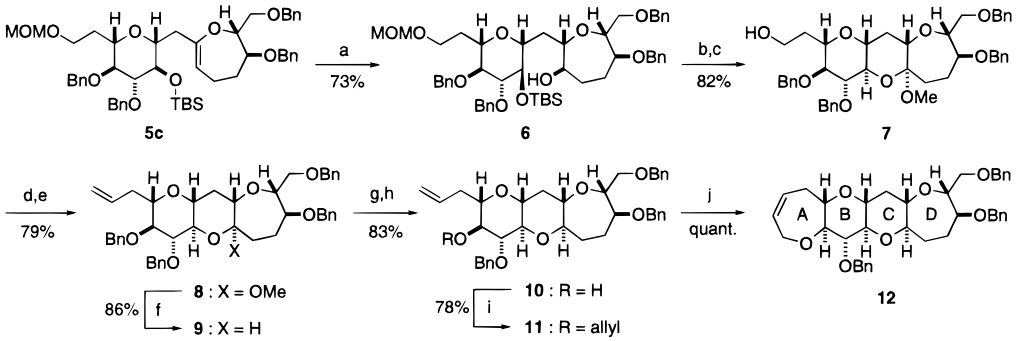
(10) Satake, M.; Murata, M.; Yasumoto, T. *Tetrahedron Lett.* **1993**, *34*, 1975.

(11) Satake, M.; Fukui, M.; Legrand, A.-M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* **1998**, *39*, 1197.

(12) Synthetic scheme for compound **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 → 0 °C, then H_2O_2, NaOH; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → r.t.; (c) TsOH, MeOH−CH_2Cl_2 (4:1), r.t. → 55 °C; (d) SO_3·Pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C → r.t.; (e) $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C; (f) Et_3SiH, BF_3·OEt_2, CH_2Cl_2−CH_3CN (5:3), r.t.; (g) I_2, CH_2Cl_2, 0 °C → r.t.; (h) Zn, AcOH, Et_2O−MeOH, r.t.; (i) NaHMDS, allyl bromide, DMF, 0 °C → r.t.; (j) $RuCl_2$(=CHPh)$(PCy_3)_2$, CH_2Cl_2, 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 $NaHCO_3$ as a milder base instead of K_3PO_4 (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 $Pd_2(dba)_3$·$CHCl_3$ 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 eight-membered 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 Et_3SiH−BF_3·OEt_2 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 [$RuCl_2$(=CHPh)$(PCy_3)_2$][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 cross-coupling 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.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Area 08245103 from the Ministry of Education, Science, Sports and Culture, Japan.

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 ^{13}C NMR spectra for compound **12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL990885N

(14) (a) Tsushima, K.; Araki, K.; Murai, A. *Chem. Lett.* **1989**, 1313. (b) Tsushima, K.; Murai, A. *Chem. Lett*. **1990**, 761. (c) Barber, C.; Jarowicki, K.; Kocienski, P. *Synlett* **1991**, 197.

(15) Reaction of the seven-membered ketene acetal triflate corresponding to **4c** [aqueous 1 M $NaHCO_3$ (3 equiv), $Pd_2(dba)_3$·$CHCl_3$ (0.05 equiv), Ph_3-As (0.4 equiv), DMF, r.t. 20 h] gave **5c** in only 29% yield.

(16) Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678.

(17) Schwab, R. R.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(18) The relative stereochemistry of **22** was firmly established by prominent NOEs between H-8/H-12, H-9/H-5 and H-9/H-11 (CTX3C numbering).