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# Studies toward the Total Synthesis of Gymnocin A, a Cytotoxic Polyether: A Highly Convergent Entry to the F–N Ring Fragment

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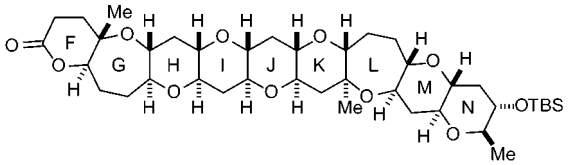
## ABSTRACT




**An efficient and highly convergent synthesis of the FGHIJKLMN ring fragment of gymnocin A, a cyctotoxic polycyclic ether isolated from the notorious red-tide forming dinoflagellate *Gymnodinium mikimotoi*, has been achieved. The present synthesis relied on extensive use of the *B*-alkyl Suzuki–Miyaura coupling reaction.**

Gymnocin A (**1**) was recently isolated from the notorious red-tide forming dinoflagellate *Gymnodinium mikimotoi* by Satake et al.[1] The toxin displays in vitro cytotoxicity against a murine P388 lymphocytic leukemia cell line ($EC_{50}$ = 1.3 $\mu$g/mL).[2] The structure of gimnocin A, including the relative and absolute stereochemistry, has been determined by a combination of NMR analyses, FAB collision induced dissociation (CID) MS/MS experiments, and a modified Mosher method (Figure 1).[1] Structurally, gymnocin A consists of 14 contiguous and saturated ether rings, including two repeating 6/6/7/6/6 ring systems, and a 2-methyl-2-butenal side chain. The number of the contiguous ether rings is the largest among the polycyclic ethers known to date.[3] Given the structural complexity, intriguing biological activity, and our continuing interest in the synthesis of polycyclic ether marine toxins based on *B*-alkyl Suzuki−Miyaura coupling,[4−6] we have been engaged in the synthesis of gymnocin A. Herein we describe a highly convergent synthesis of the FGHIJKLMN ring fragment **3** that relies on extensive use of the *B*-alkyl Suzuki−Miyaura coupling-based methodology.

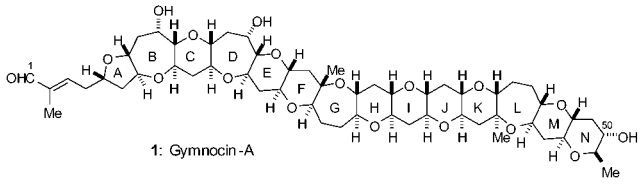



**Figure 1.** Structure of Gymnocin A (**1**).

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(1) (a) Satake, M.; Ofuji, K.; Shoji, M.; Oshima, Y.; Yasumoto, T. *Paper Abstracts*; 2000 International Chemical Congress of Pacific Basin Societies (Pacifichem 2000), Honolulu, HI, 2000; ORGN-1780. (b) Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. Submitted.

(2) Analogues of **1** of yet unknown structures showed far stronger cyctotoxicity than **1**; a private communication from Prof. M. Satake of Tohoku University.

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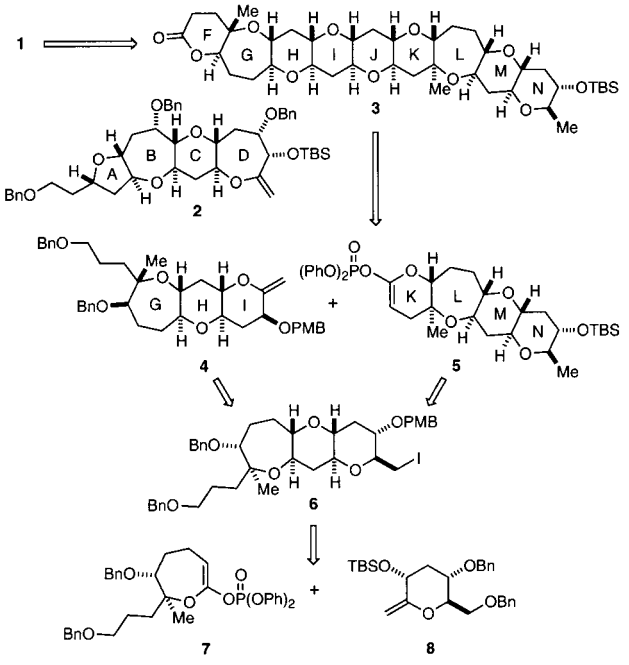
Retrosynthetically, gymnocin A (**1**) can be disconnected at the E ring into the ABCD and FGHIJKLMN fragments (**2** and **3**, respectively) that could be joined via *B*-alkyl Suzuki−Miyaura coupling (Scheme 1). We envisioned that

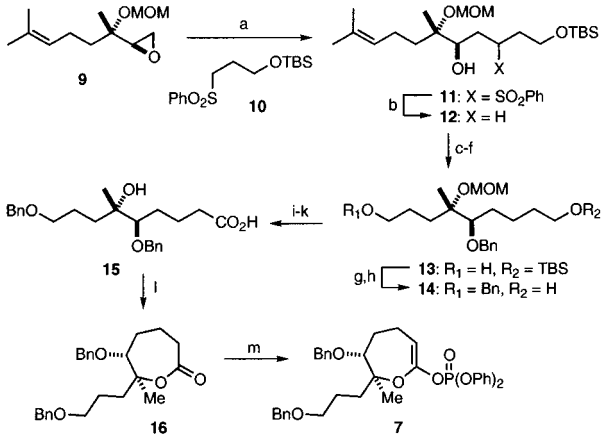
**Scheme 1.** Retrosynthetic Analysis of Gymnocin A (**1**)



the latter compound could be further divided into two fragments, the GHI (**4**) and KLMN (**5**) rings, both of which would be derived from a common precursor, **6**. The key intermediate **6**, in turn, could be prepared by convergent union of monocyclic units **7** and **8**.

The synthesis of enol phosphate **7** commenced with the known epoxide **9**,[7] derived from geraniol (Scheme 2). Reaction of **9** with a lithium anion, generated from sulfone

**Scheme 2**[a]

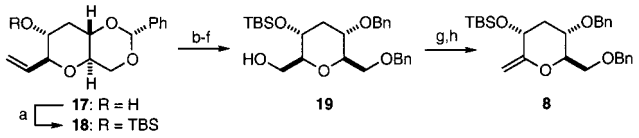


[a] Reagents and conditions: (a) **10**, *n*-BuLi, THF/HMPA, −78 °C; then **9**, 96%; (b) Na(Hg), $NaH_2PO_4$, MeOH, rt, 75%; (c) KO*t*-Bu, BnBr, THF, rt; (d) $OsO_4$, NMO, acetone/$H_2O$, rt; (e) $NaIO_4$, THF/$H_2O$, rt; (f) $NaBH_4$, MeOH, 0 °C, 81% (four steps); (g) KO*t*-Bu, BnBr, THF, rt; (h) TBAF, THF, rt, 97% (two steps); (i) $SO_3$·pyr, $Et_3N$, DMSO, $CH_2Cl_2$, rt; (j) $NaClO_2$, $NaH_2PO_4$, 2-methyl-2-butene, *t*-BuOH/$H_2O$, 0 °C; (k) TFA, $CH_2Cl_2$, 0 °C, 62% (two steps); (l) 2,4,6-$Cl_3C_6H_2COCl$, $Et_3N$, THF, rt; then DMAP, toluene, 110 °C, 62%; (m) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

**10**,[8] gave *β*-hydroxy sulfone **11**, which upon treatment with sodium amalgam provided alcohol **12** in 72% overall yield from **9**. After protection of the alcohol as its benzyl ether, the double bond was oxidatively cleaved and the resultant aldehyde was reduced to give **13** in 81% overall yield. Alcohol **13** was then converted to **14** in two steps. Oxidation of the primary alcohol **14** to carboxylic acid by a two-step procedure followed by removal of the methoxymethyl (MOM) group with TFA afforded hydroxy acid **15** in 62% yield (three steps). Lactonization under Yamaguchi conditions provided lactone **16**, which was readily converted to the enol phosphate **7**.

Construction of exocyclic enol ether **8** began with the known alcohol **17**,[9] which was protected as the TBS ether **18** (Scheme 3). Routine protective and functional group manipulations allowed the conversion to primary alcohol **19**,

**Scheme 3**[a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 81%; (b) EtSH, $Zn(OTf)_2$, $NaHCO_3$, $CH_2Cl_2$, rt, 99%; (c) KO*t*-Bu, BnBr, THF, rt; (d) $OsO_4$, NMO, acetone/$H_2O$, rt; (e) $NaIO_4$, THF/$H_2O$, rt; (f) $NaBH_4$, MeOH, 0 °C, 83% (four steps); g) $I_2$, $PPh_3$, imidazole, $CH_2Cl_2$, rt; (h) KO*t*-Bu, THF, 0 °C, quant.

(3) For reviews on marine polycyclic ethers, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, 293−314. (c) Yasumoto, T. *Chem. Rec.* **2001**, *3*, 228−242.

(4) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027−9030. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075−1077. (c) Sasaki, M.; Noguchi, K.; Fuwa, H.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 1425−1428. (d) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron Lett.* **2000**, *41*, 8371−8375. (e) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019−3033. (f) Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1090−1093. (g) Fuwa, H.; Sasaki, M.; Tachibana, K. *Org. Lett.* **2001**, *3*, 3549−3552.

(5) For reviews on Suzuki cross-coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

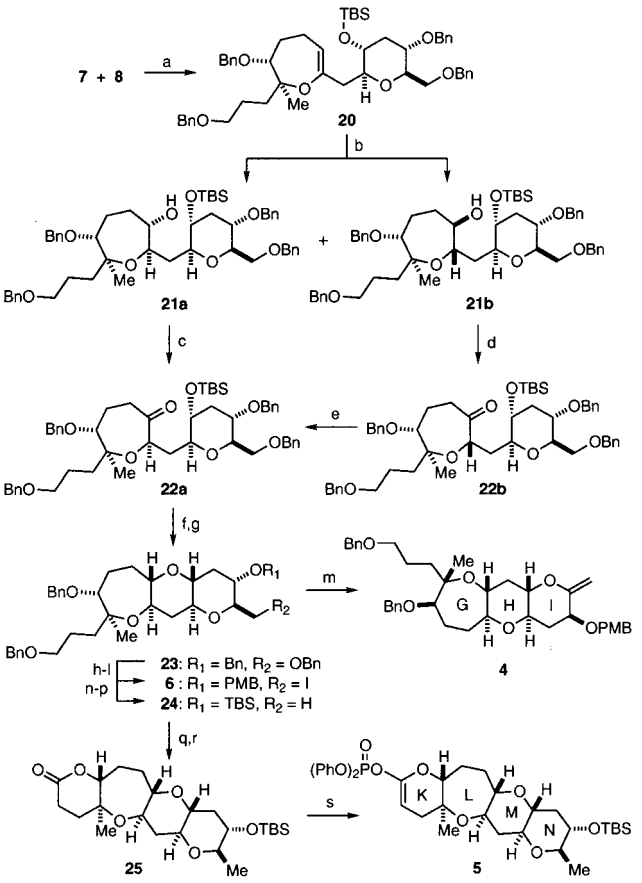
(6) For a recent comprehensive review on application of the *B*-alkyl Suzuki−Miyaura reaction in natural product synthesis, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568.

(7) Epoxide **9** is available in five steps from geraniol via Sharpless asymmetric epoxidation, see: (a) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088−5107. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

which upon iodination followed by base treatment provided the desired **8**.

Hydroboration of **8** with 9-BBN-H, followed by cross-coupling with **7** under the conditions previously optimized (aqueous $NaHCO_3$, $PdCl_2$(dppf), DMF, 50 °C)[4e] afforded the desired endocyclic enol ether **20**, but the yield was low (ca. 30%). The use of $Cs_2CO_3$ instead of $NaHCO_3$ gave a better result, and an 86% yield of **20** was obtained (Scheme 4).

**Scheme 4**[a]




[a] Reagents and conditions: (a) **8**, 9-BBN-H, THF, rt;, then aqueous $Cs_2CO_3$, **7**, $PdCl_2$(dppf), DMF, 50 °C, 86%; (b) $BH_3$·THF, THF, rt; then aqueous NaOH, $H_2O_2$, rt, **21a**: 55%, **21b**: 37%; (c) TPAP, NMO, MS4 Å, $CH_2Cl_2$, rt, 98%; (d) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, rt, 84%; (e) DBU, benzene, rt, 48% (+ recovered ketone, 48%); (f) *p*-TsOH, MeOH, rt, 84%; (g) $Et_3SiH$, $BF_3$·$OEt_2$, $CH_2Cl_2$, rt, quant; (h) $H_2$, $Pd(OH)_2$/C, MeOH, rt; (i) *p*-$MeOC_6H_4CH(OMe)_2$,PPTS, $CH_2Cl_2$, rt, 84% (two steps); (j) KO*t*-Bu, BnBr, THF, rt; (k) DIBALH, $CH_2Cl_2$, rt, 67% (two steps); (l) $I_2$, $PPh_3$, imidazole, benzene, rt, 92%; (m) KO*t*-Bu, THF, 0 °C, 91%; (n) *n*-$Bu_3SnH$, AIBN, toluene, 100 °C; (o) DDQ, $CH_2Cl_2$/phosphate buffer (pH 7), rt, 63% (two steps); (p) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 94%; (q) $H_2$, $Pd(OH)_2$/C, MeOH, rt; (r) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, rt, 61% (two steps); (s) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

Subsequent hydroboration of the enol ether moiety produced a separable mixture of the desired alcohol **21a** (55%) and the corresponding diastereomer **21b** (37%). The observed poor stereoselectivity in this reaction is presumably due to the steric hindrance of the pseudoaxial methyl group on the seven-membered ring. Oxidation of **21a** with TPAP/NMO[10] provided ketone **22a** in excellent yield. On the other hand, the undesired isomer **21b** can be converted to **22a**. Thus, **21b** was oxidized with TPAP/NMO to ketone **22b**, which upon treatment with DBU in benzene provided **22a** in 48% yield (two steps) along with the recovered **22b** (48% yield). Acidic treatment of **22a** in methanol resulted in removal of the silyl group with concomitant formation of a mixed methyl ketal in 84% yield. Exposure of the resultant methyl ketal to $Et_3SiH$ and $BF_3$·$OEt_2$[11] furnished tricyclic ether **23** as the sole product in quantitative yield. The stereostructure of **23** was established by NOE experiments as shown in Figure 2. Conversion of **23** into the key

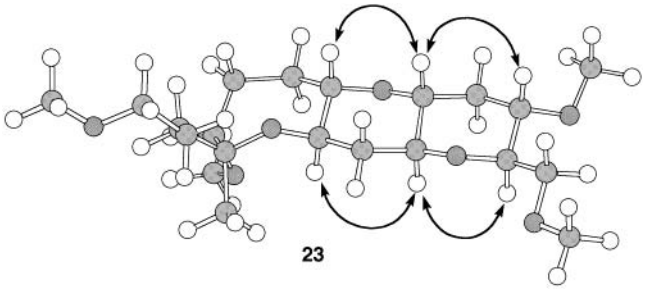



**Figure 2.** NOE experiments on compound **23** ($C_6D_6$, 500 MHz). Benzyl groups were replaced with methyl groups for clarity.

intermediate **6** was accomplished without incident in a five-step procedure as shown. Treatment of **6** with potassium *tert*-butoxide provided the GHI ring exocyclic enol ether **4** in 91% yield. On the other hand, radical reduction of **6** followed by oxidative removal of the *p*-methoxybenzyl (PMB) group and protection as its silyl ether provided **24** in 59% overall yield. The benzyl groups were removed by hydrogenolysis, and the derived diol was oxidized with TPAP/NMO to furnish lactone **25** (61% for two steps), which was then converted to enol phosphate **5**. Due to its instability, **5** was used immediately in the next coupling reaction without purification.

With the requisite coupling partners in hand, we next investigated their *B*-alkyl Suzuki−Miyaura coupling reaction (Scheme 5). Coupling of enol phosphate **5** with an alkylborane generated from **4** proceeded smoothly (aqueous $Cs_2CO_3$, $Pd(PPh_3)_4$, DMF, 50 °C), leading to the desired cross-

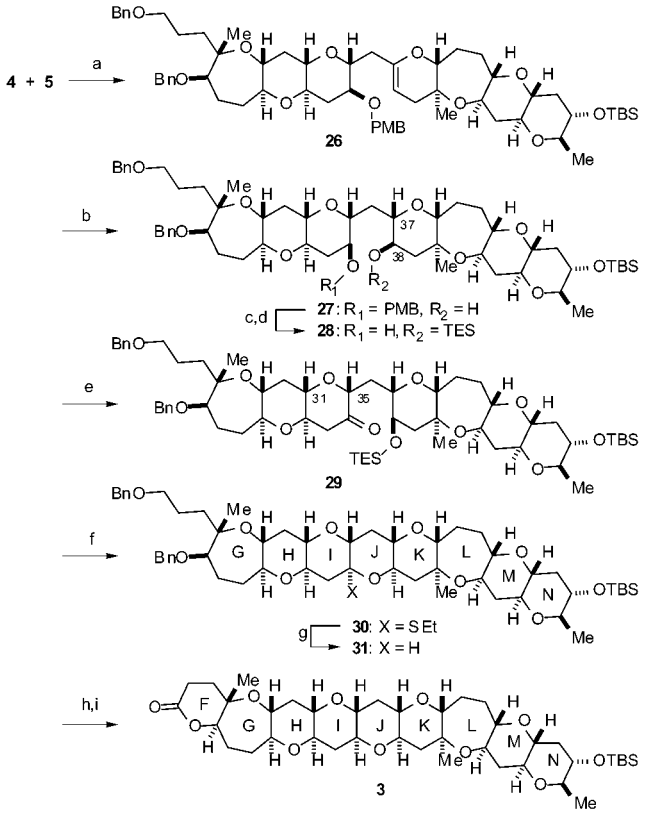
(8) Sulfone **10** was prepared from 1,3-propanediol in three steps: (i) TBSCl, $Et_3N$, $CH_2Cl_2$, rt; (ii) PhSSPh, *n*-$Bu_3P$, DMF, rt; (iii) *m*CPBA, $NaHCO_3$, $CH_2Cl_2$, 0 °C, 77% yield for three steps.

(9) Compound **17** is available in nine steps from 2-deoxy-D-ribose, see: (a) Nicolaou, K. C.; Nugiel, D. A.; Couladouros, E.; Hwang, C.-K. *Tetrahedron* **1990**, *46*, 4517−4552. (b) Reference 4e.

(10) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(11) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978.

**Scheme 5**[a]




[a] Reagents and conditions: (a) **4**, 9-BBN-H, THF, rt; then aqueous $Cs_2CO_3$, **5**, $Pd(PPh_3)_4$, DMF; (b) $BH_3$·THF, THF, −20 → 0 °C; then aqueous NaOH, $H_2O_2$, rt, 72% from **25**; (c) TESOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C, 81%; (d) DDQ, $CH_2Cl_2$/phosphate buffer (pH 7), rt, 90%; (e) TPAP, NMO, MS4 Å, $CH_2Cl_2$, 91%; (f) EtSH, $Zn(OTf)_2$, $CH_2Cl_2$, rt, 87%; (g) $Ph_3SnH$, AIBN, toluene, 100 °C, 92%; (h) $H_2$, $Pd(OH)_2$/C, EtOAc/MeOH, rt; (i) $RuCl_2(PPh_3)_3$, toluene, 93% (two steps).

coupled product **26** in good yield. Subsequent hydroboration provided alcohol **27** as the sole product in 72% overall yield (three steps from **25**). The stereochemistry at C37 and C38 positions[12] of **27** was confirmed by coupling constant analysis of the corresponding acetate derivative ($J_{37,38}$ = 9 Hz). Silylation followed by oxidative removal of the PMB group afforded alcohol **28**, which was oxidized with TPAP/NMO to afford ketone **29**. At this stage, the stereochemistry at C35 was unambiguously established by NOE between H31 and H35. Treatment of ketone **29** with EtSH and $Zn(OTf)_2$ afforded mixed thioketal **30** (87%), which was then reduced under radical conditions to yield octacyclic ether **31** in 92% yield. Finally, removal of the benzyl groups and oxidation of the resultant diol with $RuCl_2(PPh_3)_3$[13] completed the synthesis of the target FGHIJKLMN ring fragment **3** (93% yield for two steps).

In conclusion, a convergent synthesis of the FGHIJKLMN ring fragment **3** of gymnocin A (**1**) has been achieved on the basis of extensive use of the *B*-alkyl Suzuki−Miyaura coupling-based methodology. The present synthesis demonstrated the usefulness and generality of our approach to a fused polycyclic ether class of marine natural products. Synthesis of the ABCD ring fragment **2** and its coupling with **3** leading to the total synthesis of **1** is currently underway and will be reported in due course.

**Acknowledgment.** We thank Prof. M. Satake of Tohoku University for valuable discussions. This work was financially supported in part by a grant from Suntory Institute for Bioorganic Research (SUNBOR).

**Supporting Information Available:** Experimental procedures and spectral data for all new compounds; $^1H$ and $^{13}C$ NMR spectra for compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The numbering of carbon atoms of all compounds in this paper corresponds to that of gymnocin A.

(13) Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605−1608.