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

Makoto Sasaki,\*,<sup>†,‡</sup> Chihiro Tsukano,<sup>†</sup> and Kazuo Tachibana<sup>†</sup>

Department of Chemistry, Graduate School of Science, The University of Tokyo, and CREST, Japan Science and Technology Corporation (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Laboratory of Biostructural Chemistry, Graduate School of Life Science, Tohoku University, Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan

msasaki@bios.tohoku.ac.j

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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.<sup>1</sup> The toxin displays in vitro cytotoxicity against a murine P388 lymphocytic leukemia cell line (EC<sub>50</sub> = 1.3  $\mu$ g/mL).<sup>2</sup> 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).<sup>1</sup> 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.<sup>3</sup> 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,<sup>4–6</sup> 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).

<sup>&</sup>lt;sup>†</sup> The University of Tokyo and CREST, JST.

<sup>&</sup>lt;sup>‡</sup> Tohoku University.

<sup>(1) (</sup>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.

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

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



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

(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.



<sup>*a*</sup> Reagents and conditions: (a) **10**, *n*-BuLi, THF/HMPA, -78 °C; then **9**, 96%; (b) Na(Hg), NaH<sub>2</sub>PO<sub>4</sub>, MeOH, rt, 75%; (c) KOt-Bu, BnBr, THF, rt; (d) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O, rt; (e) NaIO<sub>4</sub>, THF/H<sub>2</sub>O, rt; (f) NaBH<sub>4</sub>, MeOH, 0 °C, 81% (four steps); (g) KOt-Bu, BnBr, THF, rt; (h) TBAF, THF, rt, 97% (two steps); (i) SO<sub>3</sub>·pyr, Et<sub>3</sub>N, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, rt; (j) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>, 2-methyl-2-butene, *t*-BuOH/H<sub>2</sub>O, 0 °C; (k) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 62% (two steps); (l) 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, Et<sub>3</sub>N, THF, rt; then DMAP, toluene, 110 °C, 62%; (m) KHMDS, (PhO)<sub>2</sub>P(O)Cl, THF/HMPA, -78 °C.

10,<sup>8</sup> gave  $\beta$ -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**,<sup>9</sup> which was protected as the TBS ether **18** (Scheme 3). Routine protective and functional group manipulations allowed the conversion to primary alcohol **19**,



<sup>*a*</sup> Reagents and conditions: (a) TBSCl, imidazole, DMF, rt, 81%; (b) EtSH, Zn(OTf)<sub>2</sub>, NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 99%; (c) KOt-Bu, BnBr, THF, rt; (d) OsO<sub>4</sub>, NMO, acetone/H<sub>2</sub>O, rt; (e) NaIO<sub>4</sub>, THF/H<sub>2</sub>O, rt; (f) NaBH<sub>4</sub>, MeOH, 0 °C, 83% (four steps); g) I<sub>2</sub>, PPh<sub>3</sub>, imidazole, CH<sub>2</sub>Cl<sub>2</sub>, rt; (h) KOt-Bu, THF, 0 °C, quant.

<sup>(3)</sup> 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.

<sup>(4) (</sup>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.

which upon iodination followed by base treatment provided the desired  $\mathbf{8}$ .

Hydroboration of **8** with 9-BBN-H, followed by crosscoupling with **7** under the conditions previously optimized (aqueous NaHCO<sub>3</sub>, PdCl<sub>2</sub>(dppf), DMF, 50 °C)<sup>4e</sup> afforded the desired endocyclic enol ether **20**, but the yield was low (ca. 30%). The use of Cs<sub>2</sub>CO<sub>3</sub> instead of NaHCO<sub>3</sub> gave a better result, and an 86% yield of **20** was obtained (Scheme 4).



<sup>*a*</sup> Reagents and conditions: (a) **8**, 9-BBN-H, THF, rt;, then aqueous  $Cs_2CO_3$ , **7**, PdCl<sub>2</sub>(dppf), DMF, 50 °C, 86%; (b) BH<sub>3</sub>·THF, THF, rt; then aqueous NaOH, H<sub>2</sub>O<sub>2</sub>, rt, **21a**: 55%, **21b**: 37%; (c) TPAP, NMO, MS4 Å, CH<sub>2</sub>Cl<sub>2</sub>, rt, 98%; (d) TPAP, NMO, MS 4 Å, CH<sub>2</sub>Cl<sub>2</sub>, rt, 84%; (e) DBU, benzene, rt, 48% (+ recovered ketone, 48%); (f) *p*-TsOH, MeOH, rt, 84%; (g) Et<sub>3</sub>SiH, BF<sub>3</sub>·OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, quant; (h) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt; (i) *p*-MeOC<sub>6</sub>H<sub>4</sub>CH (OMe)<sub>2</sub>,PPTS, CH<sub>2</sub>Cl<sub>2</sub>, rt, 67% (two steps); (j) KOt-Bu, BnBr, THF, rt; (k) DIBALH, CH<sub>2</sub>Cl<sub>2</sub>, rt, 67% (two steps); (l) L<sub>2</sub>, PPh<sub>3</sub>, imidazole, benzene, rt, 92%; (m) KOt-Bu, THF, 0 °C, 91%; (n) *n*-Bu<sub>3</sub>SnH, AIBN, toluene, 100 °C; (o) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/phosphate buffer (pH 7), rt, 63% (two steps); (p) TBSOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 94%; (q) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, rt; (r) TPAP, NMO, MS 4 Å, CH<sub>2</sub>Cl<sub>2</sub>, rt, 61% (two steps); (s) KHMDS, (PhO)<sub>2</sub>P(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<sup>10</sup> 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<sub>3</sub>SiH and BF<sub>3</sub>•OEt<sub>2</sub><sup>11</sup> 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 fivestep 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  $Cs_2$ -CO<sub>3</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>, DMF, 50 °C), leading to the desired cross-

<sup>(8)</sup> Sulfone **10** was prepared from 1,3-propanediol in three steps: (i) TBSC1,  $Et_3N$ ,  $CH_2Cl_2$ , rt; (ii) PhSSPh, *n*-Bu<sub>3</sub>P, DMF, rt; (iii) *m*CPBA, NaHCO<sub>3</sub>,  $CH_2Cl_2$ , 0 °C, 77% yield for three steps.

<sup>(9)</sup> 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.

<sup>(10)</sup> Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Synthesis 1994, 639–666.

<sup>(11)</sup> Lewis, M. D.; Cha, J. K.; Kishi, Y. J. Am. Chem. Soc. 1982, 104, 4976-4978.



<sup>*a*</sup> Reagents and conditions: (a) **4**, 9-BBN-H, THF, rt; then aqueous  $Cs_2CO_3$ , **5**, Pd(PPh\_3)\_4, DMF; (b) BH<sub>3</sub>·THF, THF,  $-20 \rightarrow 0$  °C; then aqueous NaOH, H<sub>2</sub>O<sub>2</sub>, rt, 72% from **25**; (c) TESOTf, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 81%; (d) DDQ, CH<sub>2</sub>Cl<sub>2</sub>/phosphate buffer (pH 7), rt, 90%; (e) TPAP, NMO, MS4 Å, CH<sub>2</sub>Cl<sub>2</sub>, 91%; (f) EtSH, Zn(OTf)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 87%; (g) Ph<sub>3</sub>SnH, AIBN, toluene, 100 °C, 92%; (h) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, EtOAc/MeOH, rt; (i) RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>, 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<sup>12</sup> 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)<sub>2</sub> 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<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub><sup>13</sup> 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.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds; <sup>1</sup>H and <sup>13</sup>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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<sup>(12)</sup> The numbering of carbon atoms of all compounds in this paper corresponds to that of gymnocin A.

<sup>(13)</sup> Tomioka, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605–1608.