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Total Synthesis of Gymnocin-A

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Gymnocin-A (**1**) is a polyether toxin isolated by Satake and coworkers in 2001 from the notorious red tide dinoflagellate, *Karenia mikimotoi*, which is a representative species that causes devastating damage worldwide.[1] The toxin is a rare polyether natural product that displays in vitro cytotoxicity against P388 leukemia cells (EC_{50} = 1.3 μg mL^{-1}).[2] The structure of gymnocin-A, including the relative and absolute stereochemistry, has been established by a combination of extensive 2D-NMR analyses, FAB collision-induced dissociation MS/MS experiments, and modified Mosher's method (Figure 1).[1] Structurally, gymnocin-A is characterized by 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 contiguous ether rings exceeds those of other polyethers hitherto synthesized.[3,4] The structural complexity as well as intriguing biological activity compelled us to embark on a program aimed at its total synthesis. Herein, we describe a convergent and efficient total synthesis of gymnocin-A, which is realized by extensive use of our developed *B*-alkyl Suzuki−Miyaura coupling-based methodology.[5−7]

The retrosynthetic plan is outlined in Scheme 1. Clearly, construction of the large polyether skeleton constituted the major challenge in the synthesis of **1**. Simplification of the 2-methyl-2-butenal side chain in **1** would lead to tetradecacyclic polyether core **2**, which was envisioned to arise from convergent coupling of the ABCD and FGHIJKLMN ring fragments (**3**[8b] and **4**,[8a] respectively) through the *B*-alkyl Suzuki−Miyaura coupling-based strategy.[4] Following their convergent union, stereoselective introduction of the C17 hydroxyl group and reductive ring closure of the E ring would complete the assembly of the polyether skeleton.

Enol triflate **4** required for cross-coupling with **3** was obtained from lactone **5** through kinetic deprotonation (KHMDS, THF/HMPA, −78 °C) and triflate formation by use of Comins' reagent[9] (Scheme 2). Suzuki−Miyaura coupling of the alkylborane derived from exocyclic enol ether **3** (9-BBN, THF, room temperature) with **4** proceeded smoothly in the presence of aqueous Cs_2CO_3 and Pd(PPh_3)$_4$ in DMF at room temperature to produce the desired cross-coupled product **6** in excellent yield (81%). Subsequent hydroboration of endocyclic enol ether **6** with a borane−dimethyl sulfide complex in THF proceeded stereoselectively (75%).[10] The resulting secondary alcohol **7**[11] was protected as the TES ether, and the PMB group was oxidatively removed to afford alcohol **8** in 79% yield for the two steps. For the introduction of the C17 hydroxyl group, alcohol **8** was oxidized with TPAP/NMO[12] to give ketone **9** in 95% yield. Conversion to the corresponding silyl enol ether followed by oxidation with OsO_4/NMO installed the C17 hydroxyl group, and subsequent protection of the resultant alcohol delivered the desired α-siloxy ketone **10**[11] as a single stereoisomer in high overall yield.

With ketone **10** in hand, ring-closure to mixed thioketal **12** was next investigated. In contrast to precedent methodology,[8a] treatment of **10** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2 resulted in only a low yield of **12**. After some experiments, it was found that the choice of solvent was critical for this cyclization. Use of nitromethane as a solvent produced the desired mixed thioketal **12** and its desilylated product **11** in 38 and 40% yield, respectively. The latter compound was resilylated to **12** in 71% yield. Finally, reductive desulfurization of **12** was achieved under radical conditions (Ph_3SnH, AIBN, toluene, 110 °C)[13] to furnish the target polyether core **2** in excellent yield.

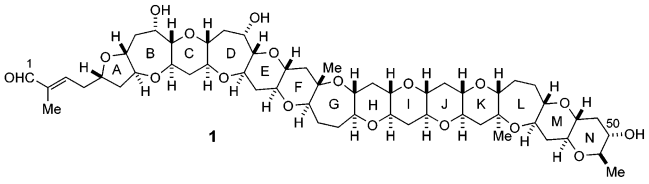
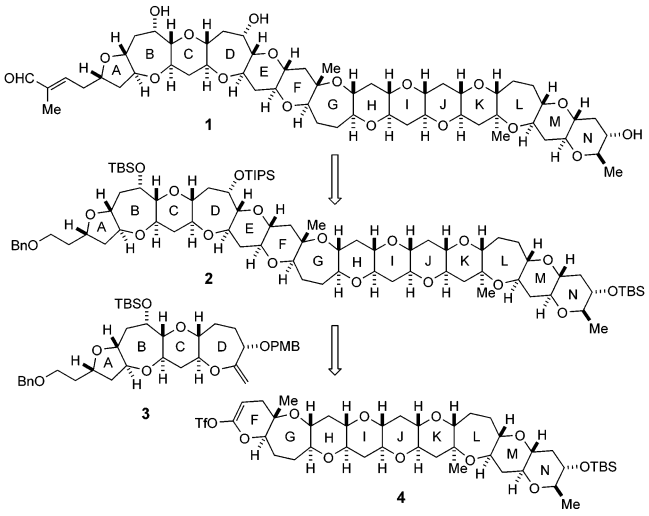


Figure 1. Structure of gymnocin-A.

Scheme 1. Retrosynthetic Plan for Gymnocin-A



The last stage of the synthesis involved the incorporation of a 2-methyl-2-butenal side chain. Since attempts to cleave the TBS and TIPS groups at the ultimate step of our initial total synthesis effort were fruitless, the TBS and TIPS groups were exchanged for TES at the stage of **2**. Subsequent reductive removal of the benzyl ether with LiDBB[14] afforded primary alcohol **13** in 73% overall yield from **2**. Oxidation with TPAP/NMO followed by Wittig reaction of the derived aldehyde with methyl 2-(triphenylphosphoranilidene)propionate and subsequent reduction with DIBAL-H generated allylic alcohol **14** in 66% overall yield. Finally, removal of the TES groups with tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF)[15] in THF/DMF was followed by chemoselective oxidation of the allylic alcohol moiety with MnO_2 to furnish gymnocin-A (**1**) in 91% yield for the two steps. The

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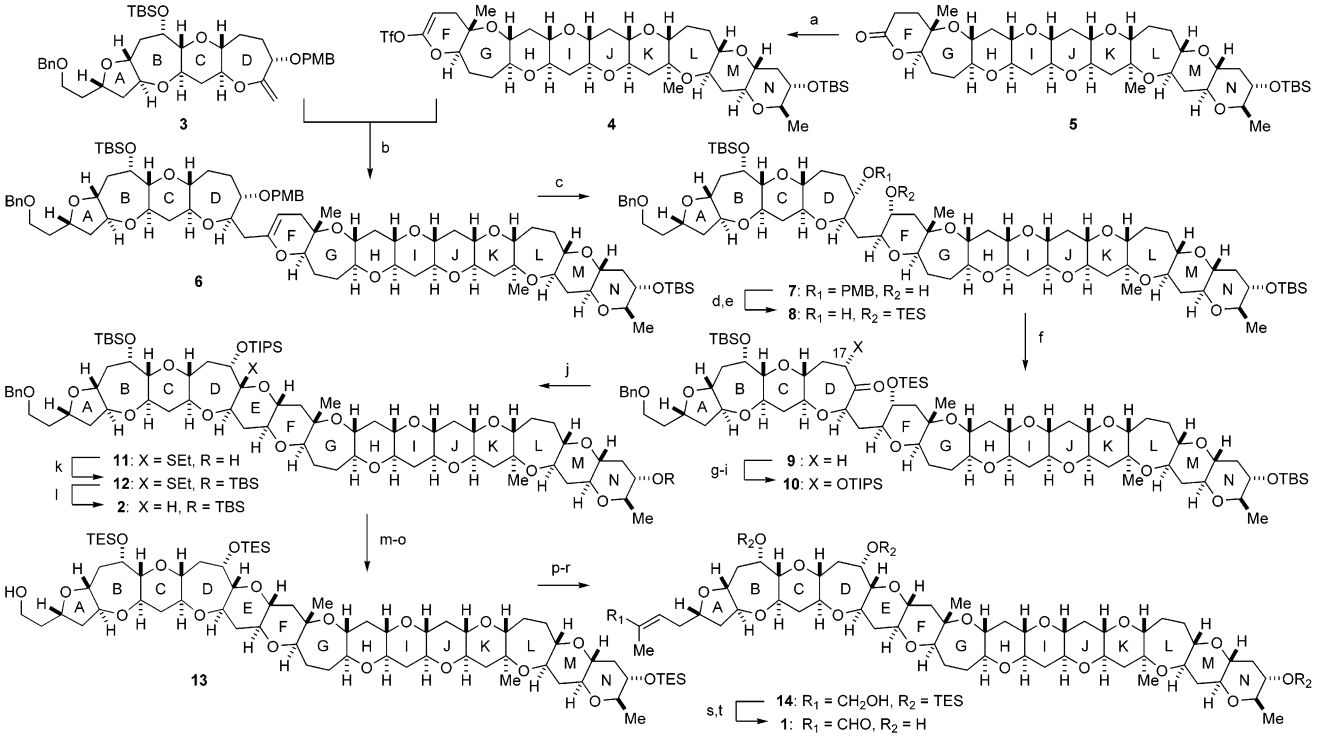
Scheme 2 [a]



[a] Reagents and conditions: (a) KHMDS, THF/HMPA, −78 °C, Comins' reagent, −78 → 0 °C, 80%; (b) **3**, 9-BBN, THF, rt, then **4**, 3M Cs_2CO_3, $Pd(PPh_3)_4$, DMF, rt, 81%; (c) BH_3•SMe_2, THF, 0 °C → rt, then NaOH, H_2O_2, rt, 75%; (d) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (e) DDQ, CH_2Cl_2/pH 7 phosphate buffer, 0 °C, 79% (two steps); (f) TPAP, NMO, 4Å MS, CH_2Cl_2, rt, 95%; (g) LiHMDS, TMSCl, Et_3N, THF, −78 °C; (h) OsO_4, NMO, THF/H_2O, rt; (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 85% (three steps); (j) EtSH, $Zn(OTf)_2$, $MeNO_2$, 0 °C → rt, **11**: 40%; **12**: 38%; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 71%; (l) Ph_3SnH, AIBN, toluene, 110 °C, 98%; (m) TBAF, 4Å MS, MeCN, 70 °C; (n) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (o) LiDBB, THF, −78 °C, 73% (three steps); (p) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (q) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, rt; (r) DIBAL-H, CH_2Cl_2, −78 °C, 66% (three steps); (s) TASF, THF/DMF, 0 °C → rt; (t) MnO_2, $CHCl_3$, rt, 91% (two steps).

synthetic gymnocin-A was identical to the natural sample by ^1H and ^{13}C NMR and MS spectra, thus confirming the structure of gymnocin-A.

In conclusion, we have accomplished the first total synthesis of gymnocin-A, a marine polyether with the largest number of contiguous ether rings. The synthesis heavily relied on the *B*-alkyl Suzuki−Miyaura coupling-based strategy, which undoubtedly is an important and general fragment-coupling process in polyether synthesis. Extension of this chemistry to the synthesis of structural analogues of gymnocin-A to explore the structure−activity relationship is currently under way and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, stereochemical determination for compounds **7** and **10**, and comparison data for natural and synthetic gymnocin-A (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett*. **2002**, *43*, 5829.
(2) While the structures were not disclosed, congeners of **1** displayed far stronger cytotoxicity than **1**; a private communication from Prof. M. Satake of Tohoku University.
(3) For reviews on marine polyethers, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev*. **1993**, *93*, 1897. (b) Murata, M.; Yasumoto, T. *Nat. Prod. Rep*. **2000**, *17*, 293. (c) Yasumoto, T. *Chem. Rec*. **2001**, *3*, 228.
(4) For total synthesis of large polyether natural products, see: (a) Brevetoxin B: Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc*. **1995**, *117*, 1173. (b) Brevetoxin A: Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gatner, P. *Nature* **1998**, *392*, 264. (c) Ciguatoxin CTX3C: Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.
(5) (a) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett*. **1998**, *39*, 9027. (b) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett*. **1999**, *1*, 1075. (c) Fuwa, H.; Sasaki, M.; Tachibana, K. *Tetrahedron* **2001**, *57*, 3019. (d) Fuwa, H.; Sasaki, M.; Tachibana, K. *Org. Lett*. **2001**, *3*, 3549. (e) Sasaki, M.; Ishikawa, M.; Fuwa, H.; Tachibana, K. *Tetrahedron* **2002**, *58*, 1889. (f) Takakura, H.; Sasaki, M.; Honda, S.; Tachibana, K. *Org. Lett*. **2002**, *4*, 2771. (g) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc*. **2002**, *124*, 14983 and references therein.
(6) For reviews on Suzuki−Miyaura coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem*. **1999**, *576*, 147. (c) Suzuki, A.; Brown, H. C. *Organic Syntheses Via Boranes*; Aldrich Chem. Co. Inc.: Wisconsin, 2003; Vol. 3.
(7) 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.
(8) (a) Sasaki, M.; Tsukano, C.; Tachibana, K. *Org. Lett*. **2002**, *4*, 1747. (b) Sasaki, M.; Tsukano, C.; Tachibana, K. *Tetrahedron Lett*. **2003**, *44*, 4351.
(9) Comins, D.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299.
(10) For similar stereoselective hydroboration, see ref 8a.
(11) For stereochemical determination for compounds **7** and **10**, see Supporting Information.
(12) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(13) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc*. **1989**, *111*, 5321. See also refs 4d, f, g, and 7.
(14) (a) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem*. **1980**, *45*, 1924. (b) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc*. **1988**, *110*, 854.
(15) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc*. **1980**, *102*, 1223. (b) Sheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem*. **1998**, *63*, 6436.

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