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Synthetic entry to the ABCD ring fragment of gymnocin-A, a cytotoxic marine polyether

Makoto Sasaki,[a,*] Chihiro Tsukano[b] and Kazuo Tachibana[b]

[a]*Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University, Tsutsumidori-Amamiya, Aoba-ku, Sendai 981-8555, Japan*

[b]*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*

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Abstract—Synthetic entry to the ABCD ring fragment of gymnocin-A, a cytotoxic marine polyether, has been achieved based on the *B*-alkyl Suzuki–Miyaura coupling-based strategy and radical cyclization for the construction of the tetrahydrofuran ring A.
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Gymnocin-A (**1**) was recently isolated from the notorious red tide dinoflagellate, *Karenia mikimotoi*, by Satake and co-workers.[1] The toxin displays in vitro cytotoxicity against P388 cancer cells ($EC_{50}=1.3$ μg/mL).[1,2] The structure of gymnocin-A, including the relative and absolute stereochemistry, has been determined by a combination of NMR analyses, FAB collision-induced dissociation MS/MS experiments, and modified Mosher's method (Fig. 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 polycyclic ethers hitherto known.[3] Given the structural complexity along with intriguing biological activity, we have been engaged in the synthesis of gymnocin-A, culminating in the synthesis of the FGHIJKLMN ring fragment **3** (Scheme 1).[4] Herein we describe a synthetic route to the ABCD ring fragment **2** that features the *B*-alkyl Suzuki–Miyaura coupling of the B and D rings[5–7] and radical cyclization for constructing the A ring.

Assembly of the BCD ring system began with the preparation of exocyclic enol ether **7** (Scheme 2). Seven-membered lactone **4** was converted to alcohol **5** through Pd(0)-mediated carbonylation of the corresponding enol phosphate.[8,9] Desilylation with tetra-*n*-butylammonium fluoride (TBAF) followed by benzylation and reductive opening of the anisilydene acetal gave alcohol **6** (78% overall yield), which was readily converted to exocyclic enol ether **7** via iodination and base treatment (91% for the two steps).

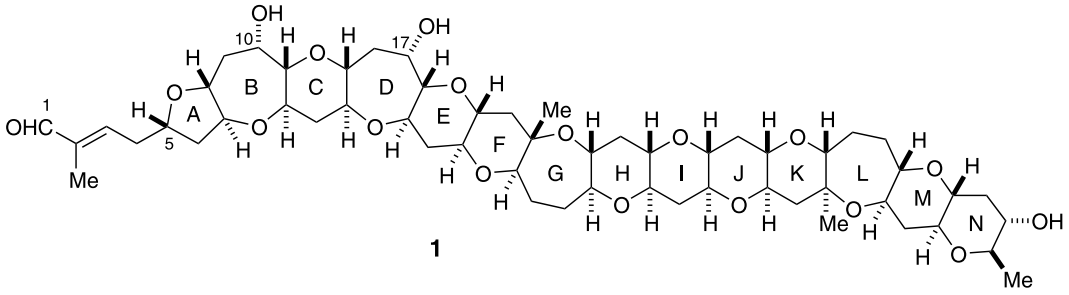

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Figure 1. Structure of gymnocin-A.

Keywords: gymnocin-A; polycyclic ethers; *B*-alkyl Suzuki–Miyaura coupling; radical cyclization.
* Corresponding author. Tel.: +81-22-717-8828; fax: +81-22-717-8897; e-mail: msasaki@bios.tohoku.ac.jp

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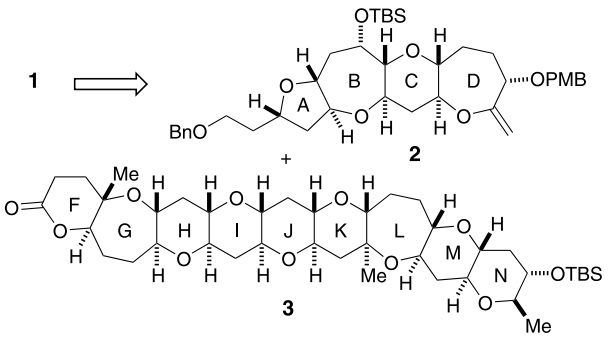
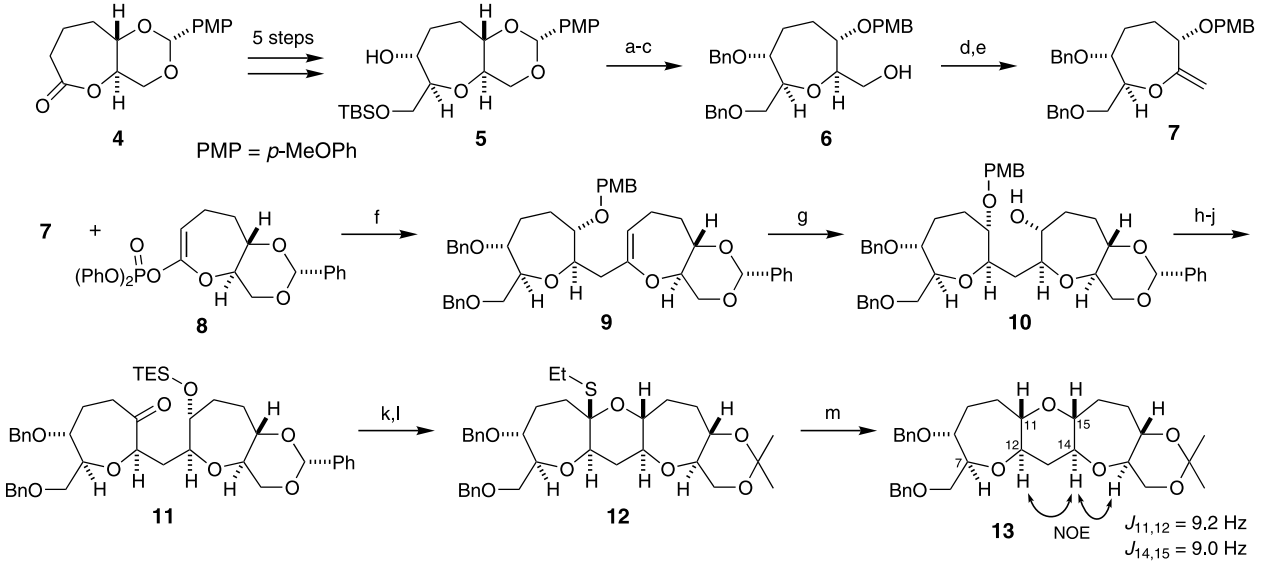


Scheme 1. Retrosynthetic analysis of gymnocin-A (**1**).

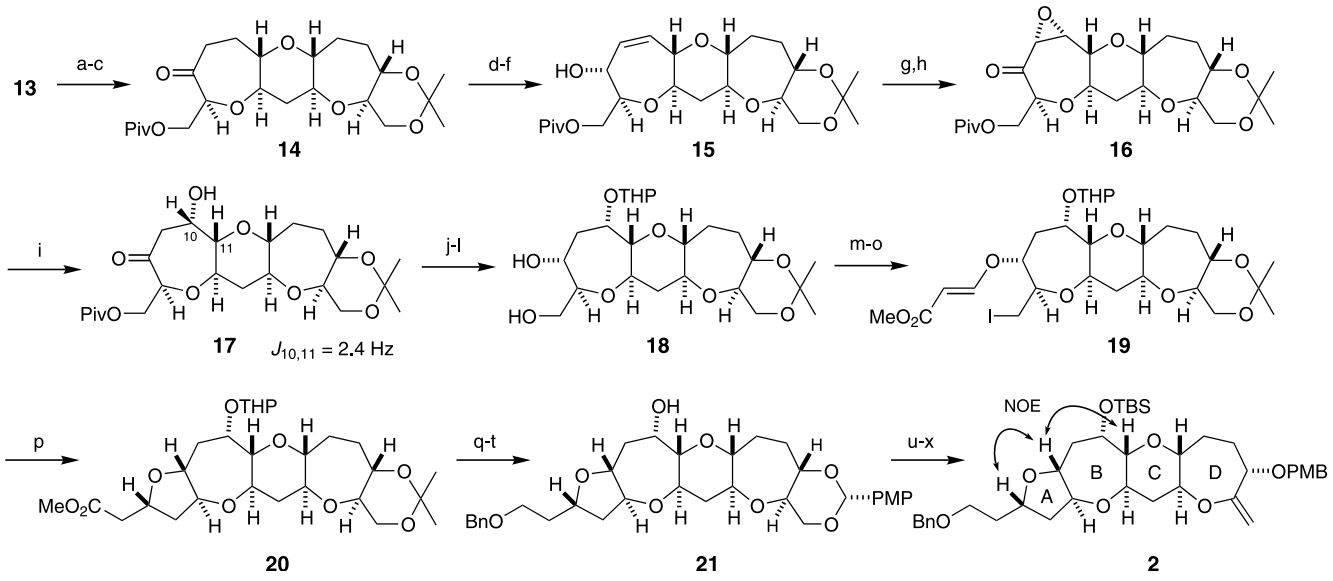
Hydroboration of **7** with 9-BBN and in situ coupling of the derived alkylborane with enol phosphate **8**[5h] provided cross-coupled product **9** (1 M aqueous $NaHCO_3$, $Pd(PPh_3)_4$, DMF, 50°C). Subsequent hydroboration of the enol ether moiety ($BH_3{\cdot}SMe_2$, then H_2O_2, NaOH) gave the desired alcohol **10** in 54% overall yield from **7**, along with the diastereomeric alcohol (not shown, 12% from **7**). Protection of **10** as its triethylsilyl (TES) ether, oxidative removal of the *p*-methoxybenzyl (PMB) group, and oxidation of the resultant alcohol with TPAP/NMO[10] gave ketone **11** in 86% overall yield.[11] Treatment of **11** with EtSH and $Zn(OTf)_2$ effected removal of the TES and benzylidene acetal groups and concomitant mixed thioketal formation. The resulting diol was reprotected as the acetonide to give **12** in 87% yield for the two steps. Finally, desulfurization under radical conditions[4,5f,g,i,j,12] furnished tricyclic ether **13** in 93% yield. The stereostructure of **13** was unambiguously confirmed by NOEs and coupling constants as shown.

With the requisite **13** in hand, we next focused on introduction of the C10[13] hydroxyl group (Scheme 3). Thus, reductive removal of the benzyl groups within **13** with lithium di-*tert*-butylbiphenylide (LiDBB)[14] was followed by selective protection of the primary hydroxyl group as the pivalate ester (85% overall yield). The residual secondary alcohol was then oxidized to ketone **14** in 94% yield. Conversion to the enone via the Ito–Saegusa protocol[15] and subsequent Luche reduction[16] gave allylic alcohol **15** in 84% overall yield. Directed epoxidation with *m*CPBA followed by oxidation gave α,β-epoxy ketone **16** (67% yield for the two steps), which was then reduced with $Na[PhSeB(OEt)_3]$[17] to provide β-hydroxy ketone **17** in quantitative yield. The stereochemistry of the C10 hydroxyl group was assigned by the small coupling constant, $J=2.4$ Hz, between 10-H and 11-H. Protection of the hydroxyl group as its tetrahydropyranyl (THP) ether followed by stereoselective reduction of the ketone with L-Selectride® and removal of the pivalate ester gave diol **18** in 85% yield for the three steps.

For construction of the 2,3-disubstituted tetrahydrofuranyl ring A, we envisioned radical cyclization of β-alkoxy acrylate.[18,19] Thus, regioselective tosylation of the primary hydroxyl group of **18** (81% yield) followed by reaction of the residual secondary alcohol with methyl propiolate in the presence of *N*-methyl morpholine (NMM) afforded β-alkoxy acrylate, which was then treated with sodium iodide in reflux acetone to give a radical cyclization precursor, iodide **19** (72% yield for the two steps). Treatment of **19** with tributylstannane in the presence of triethylborane[20] in toluene at −78°C effected cyclization of the tetrahydrofuranyl ring to provide **20** in nearly quantitative yield. Ester **20**



Scheme 2. *Reagents and conditions*: (a) TBAF, THF, rt; (b) KO*t*-Bu, BnBr, THF, rt; (c) DIBALH, CH_2Cl_2, 0°C, 78% (three steps); (d) I_2, PPh_3, imidazole, THF, rt, 95%; (e) KO*t*-Bu, THF, 0°C, 96%; (f) **7**, 9-BBN, THF, rt, then 1 M aq. $NaHCO_3$, $Pd(PPh_3)_4$, **8**, DMF, 50°C; (g) $BH_3{\cdot}SMe_2$, THF, rt, then H_2O_2, NaOH, 0°C→rt, 54% (two steps); (h) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 89%; (i) DDQ, pH 7.0 phosphate buffer, CH_2Cl_2, rt, 97%; (j) TPAP, NMO, MS 4 Å, CH_2Cl_2, rt, quant.; (k) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt; (l) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 87% (two steps); (m) Ph_3SnH, AIBN, PhMe, 100°C, 93% (+ diastereomer, 7%).



Scheme 3. *Reagents and conditions*: (a) LiDBB, THF, −78°C; (b) PivCl, pyridine, CH_2Cl_2, rt, 85% (two steps); (c) TPAP, NMO, MS 4 Å, CH_2Cl_2, rt, 94%; (d) LiHMDS, TMSCl, Et_3N, THF, −78°C; (e) $Pd(OAc)_2$, MeCN, rt, 96% (two steps); (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/CH_2Cl_2, rt, 88%; (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 83%; (h) TPAP, NMO, MS 4 Å, CH_2Cl_2, rt, 81%; (i) $Na[PhSeB(OEt)_3]$, AcOH, EtOH, 0°C→rt, quant.; (j) DHP, CSA, CH_2Cl_2, rt, 81%; (k) L-Selectride®, THF, −78°C; (l) $LiAlH_4$, THF, 0°C, 85% (three steps); (m) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 81%; (n) methyl propiolate, NMM, CH_2Cl_2, 35°C; (o) NaI, acetone, reflux, 72% (two steps); (p) Bu_3SnH, Et_3B, PhMe, −78°C, quant.; (q) $LiAlH_4$, THF, 0°C; (r) KO*t*-Bu, BnBr, THF, rt; (s) CSA, MeOH, rt; (t) *p*-MeOPhCH$(OMe)_2$, CSA, CH_2Cl_2, rt, 71% (four steps); (u) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 95%; (v) DIBALH, CH_2Cl_2, 0°C, 93%; (w) I_2, PPh_3, imidazole, THF, rt, 86%; (x) KO*t*-Bu, THF, 0°C, quant.

was then converted into alcohol **21** (71% overall yield) via benzylation of the resulting alcohol, acid hydrolysis of the acetal protective groups, and reprotection as the anisilydene acetal. Silylation of the C10 alcohol was followed by reductive opening of the anisilydene acetal. Iodination of the resultant primary hydroxyl group followed by base treatment furnished the desired ABCD ring exocyclic enol ether **2** in 76% overall yield.[21] The stereostructure of **2** was unambiguously established by NOE experiments as shown.

In conclusion, we have developed a synthetic route to the ABCD ring fragment **2** of gymnocin-A (**1**) utilizing the *B*-alkyl Suzuki–Miyaura coupling-based methodology and radical cyclization for constructing the A ring. Coupling of **2** with the FGHIJKLMN ring fragment leading to the total synthesis of **1** is currently under way and will be reported in due course.

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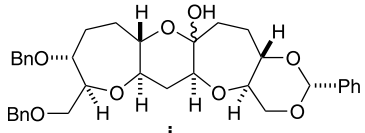
11. Oxidation of **10** followed by removal of the PMB group afforded hemiketal **i** in good yield. However, treatment of **i** with $EtSH/Zn(OTf)_2$ led to decomposition.



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21. Selected data for compound **2**: $[\alpha]_D^{19}$ −7.6 (*c* 0.98, benzene); IR (film) 2949, 2929, 2854, 1638, 1613, 1511, 1458, 1289, 1248, 1081, 1039, 836, 779, 699 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.26 (m, 2H), 7.23 (m, 2H), 7.17 (m, 2H), 7.08 (m, 1H), 6.84 (m, 2H), 4.66 (s, 1H), 4.57 (d, $J=11.5$ Hz, 1H), 4.44 (ddd, $J=9.5$, 7.8, 6.4 Hz, 1H), 4.34 (ddd, $J=11.5$, 8.9, 5.1 Hz, 1H), 4.29 (d, $J=12.6$ Hz, 1H), 4.26 (d, $J=12.6$ Hz, 1H), 4.21 (d, $J=11.5$ Hz, 1H), 4.19 (m, 1H), 4.05 (br d, $J=6.3$, 1.0 Hz, 1H), 4.00 (s, 1H), 3.97 (ddd, $J=11.9$, 8.8, 4.4 Hz, 1H), 3.89 (br d, $J=6.3$, 1.0 Hz, 1H), 3.62 (ddd, $J=8.8$, 7.8, 7.8 Hz, 1H), 3.48 (m, 1H), 3.41(m, 1H), 3.32 (s, 3H), 3.05 (ddd, $J=10.6$, 8.9, 4.6 Hz, 1H), 2.88 (br d, $J=8.8$, 1.0 Hz, 1H), 2.67 (ddd, $J=12.3$, 5.1, 4.4 Hz, 1H), 2.30 (ddd, $J=14.4$, 7.8, 6.3, 1H), 2.19 (m, 1H), 2.01 (ddd, $J=13.2$, 8.2, 6.4 Hz, 1H), 1.96–1.78 (m, 6H), 1.72 (m, 1H), 1.55 (m, 1H), 0.96 (s, 9H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 159.2, 139.4, 130.8, 129.3 (×2), 128.5 (×2), 128.3 (×2), 127.5, 114.1 (×2), 94.5, 82.6, 82.2, 80.1, 79.2, 77.4, 75.01, 74.98, 73.0, 72.0, 70.4, 69.4, 67.4, 54.7, 38.61, 38.58, 37.20, 36.98, 28.1, 27.7, 26.1 (×3), 18.3, −4.1, −5.0; HRMS (FAB) calcd for $C_{39}H_{56}O_8SiNa$ $[(M+Na)^+]$ 703.3642, found 703.3650.