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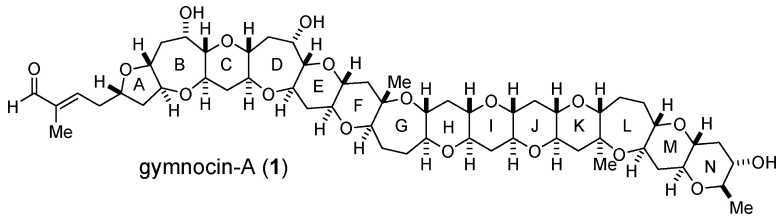

gymnocin-A (**1**)

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Convergent Total Synthesis of Gymnocin-A and Evaluation of Synthetic Analogues

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Abstract: The first total synthesis of gymnocin-A (**1**), a cytotoxic polycyclic ether isolated from a notorious red tide dinoflagellate, *Karenia mikimotoi*, has been accomplished. The synthesis relies heavily on the Suzuki−Miyaura cross-coupling-based methodology to assemble the tetradecacyclic polyether skeleton. Convergent union of the GHI (**5**) and KLMN (**6**) rings, both of which were prepared from a common intermediate **7**, and the subsequent ring closure of the J ring delivered the GHIJKLMN ring. The crucial coupling between the ABCD and FGHIJKLMN ring fragments (**3** and **4**, respectively) and stereoselective installation of the C_{17} hydroxyl group, followed by cyclization of the E ring gave rise to the tetradecacyclic polyether skeleton **2**. Finally, incorporation of the 2-methyl-2-butenal side chain completed the total synthesis of gymnocin-A. The convergent nature of the synthesis, which employs three fragments of comparable complexity, is well-suited for preparation of various structural analogues of gymnocin-A to explore the structure−activity relationship. The results of preliminary structure−activity relationship studies of several synthetic analogues are also provided.

Introduction

Since the structure of brevetoxin B, a causative agent of Florida red tides, was first reported by the Nakanishi group in 1981,[1] a large number of polycyclic ether marine natural products have been isolated and characterized to date.[2] The intriguing structural characteristics of these natural products, along with their potent and diverse biological activities, have stimulated the interest of organic chemists.[3] The strategies and methodologies developed over the past two decades have culminated in the successful total synthesis of natural polycyclic ethers, including hemibrevetoxin B,[4] brevetoxins B[5,6] and A,[7] ciguatoxin CTX3C,[8] and gambierol.[9,10]

Gymnocin-A (**1**, Figure 1) is a polycyclic ether toxin isolated by Satake and co-workers from the notorious red tide dinoflagellate, *Karenia mikimotoi*, which is a representative species that causes devastating damages worldwide.[11] The toxin is a rare polycyclic ether natural product that exhibits potent in vitro cytotoxic activity against P388 murine leukemia with IC_{50} value of 1.3 μg mL^{-1}. Several congeners of **1** were also isolated, and some of them displayed cytotoxicity far stronger than that

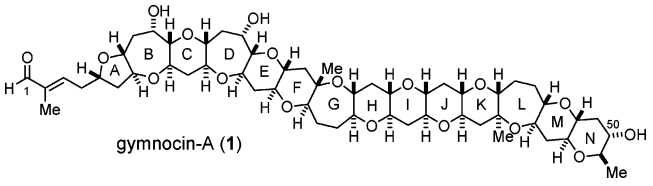

Figure 1. Structure of gymnocin-A (**1**).

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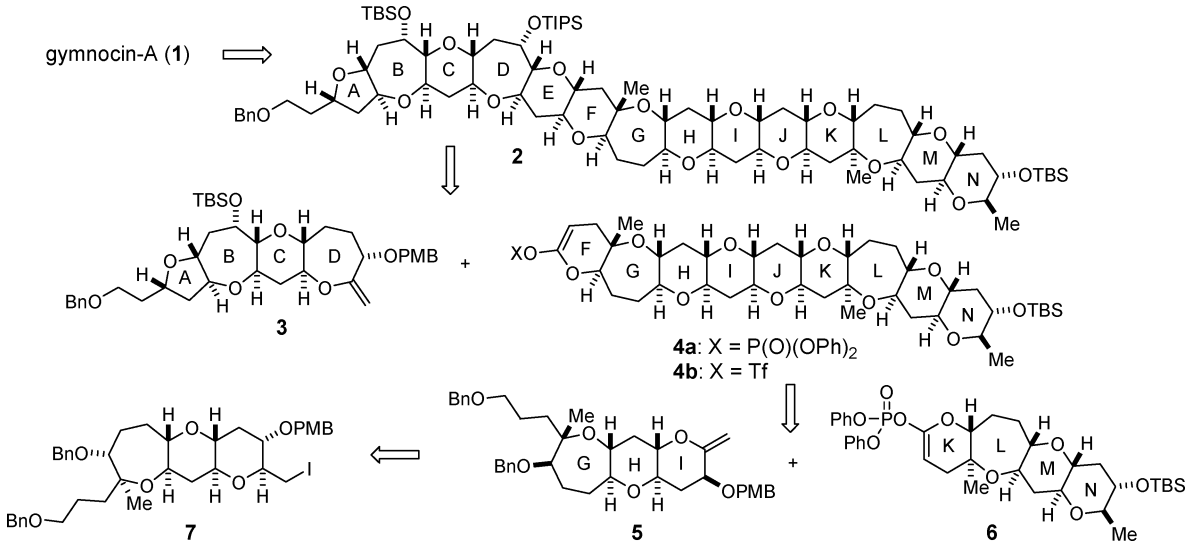
Scheme 1. Retrosynthesis Plan for Gymnocin-A (**1**)



of **1**, although their structures remained to be determined.[12] The structure of gymnocin-A, including the relative and absolute stereochemistry, has been elucidated by a combination of extensive 2D-NMR studies, FAB collision-induced dissociation MS/MS experiments, and modified Mosher ester analysis.[11] Structurally, gymnocin-A is characterized by 14 contiguous and saturated ether rings, including two repeating 6/6/7/6/6 ring systems (the EFGHI and JKLMN rings), and a 2-methyl-2-butenal side chain. The number of contiguous ether rings of **1** exceeds those of other polycyclic ethers hitherto synthesized.[4−10]

Given the structural complexity and intriguing biological activity of these polycyclic ether marine biotoxins and our continuing interest in their synthesis based on the Suzuki−Miyaura coupling methodology,[13,14] we engaged in the total synthesis of gymnocin-A. We viewed gymnocin-A as an ideal synthetic target for assessing the feasibility and generality of the Suzuki−Miyaura coupling chemistry developed in our laboratories. Furthermore, a convergent and flexible route to gymnocin-A would provide access to a diverse set of synthetic analogues, which would provide new insights into understanding the structural features responsible for the potent cytotoxic activity of gymnocins. In this study, we describe the details of our highly convergent total synthesis of gymnocin-A[15] and the results of preliminary structure−activity relationship studies.

Synthesis Plan. Our retrosynthetic plan for gymnocin-A (**1**) is illustrated in Scheme 1, in which recognition of the symmetry elements in the target molecule plays a crucial role. Clearly, construction of the large tetradecacyclic polyether skeleton **2** constituted the major challenge in the total synthesis of **1**. In this context, we planned to incorporate the enal-containing side chain at a late stage of the synthesis, and the polycyclic ether backbone **2** was envisioned to be assembled by a particularly challenging Suzuki−Miyaura cross-coupling between the ABCD and FGHIJKLMN ring fragments (**3** and **4**, respectively). Following their convergent union, stereoselective installation of the C_{17} hydroxyl group and reductive ring closure of the E ring would reach the polycyclic ether skeleton. The symmetry elements of fragment **4** allowed further disconnection at the J ring into two fragments, the GHI (**5**) and KLMN (**6**) rings. Both of these fragments then could be derived from a common precursor **7**.

Results and Discussion

Synthesis of the ABCD Ring Fragment. The initial synthetic plan for the ABCD ring fragment **3** is illustrated in Scheme 2. We envisioned constructing the tetrahydrofuran ring A by an intramolecular radical cyclization of β-alkoxyacrylate **8**. The precursor tricyclic ether **9** was, in turn, to be synthesized by the Suzuki−Miyaura coupling methodology.

Hydroboration of **10**[16] with 9-BBN (THF, room temperature (rt)) and coupling of the derived alkylborane with enol phosphate **11**[14b,f] (1 M aqueous $NaHCO_3$, $Pd(PPh_3)_4$, DMF, 50 °C) delivered the expected cross-coupled product **12** (Scheme 3). Subsequent hydroboration of the enol ether moiety (BH_3·SMe_2; then H_2O_2, NaOH) gave the desired alcohol **13** in 47% overall yield from **10**.[17] Protection of **13** as the triethylsilyl (TES) ether

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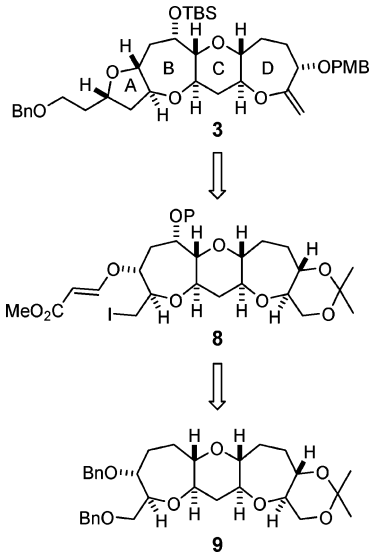
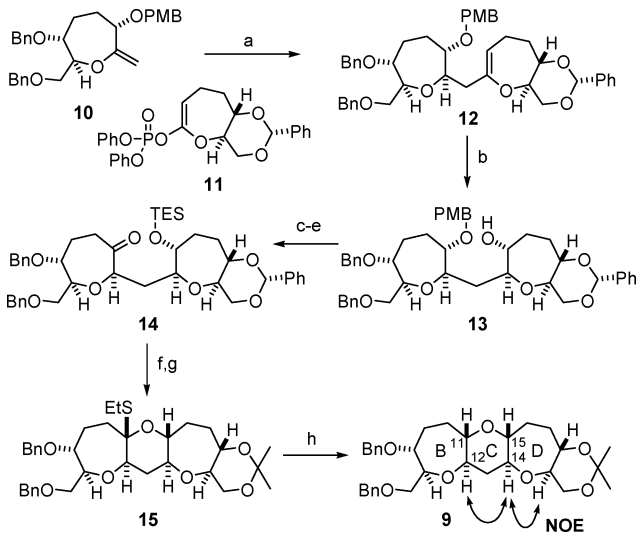
(16) Details of the synthesis of compounds **10**, **25**, **39**, and **68** are included in Supporting Information.
(17) The corresponding diastereomeric alcohol was obtained in ca. 10% yield.

Scheme 2. Initial Synthesis Plan for ABCD Ring Fragment **3**



Scheme 3 [a]



[a] Reagents and conditions: (a) **10**, 9-BBN, THF, rt; then 1 M aq $NaHCO_3$, **11**, $Pd(PPh_3)_4$, DMF, 50 °C; (b) $BH_3{\cdot}SMe_2$, THF, rt; then H_2O_2, aq NaOH, 0 °C → rt, 47% from **10**; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; (d) DDQ, pH 7.0 phosphate buffer, CH_2Cl_2, rt, 88%; (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 92%; (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt; (g) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt, 96% (two steps); (h) Ph_3SnH, AIBN, toluene, 100 °C, 78%.

and oxidative removal of the *p*-methoxybenzyl (PMB) group, followed by oxidation of the resultant alcohol with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[18] and *N*-methylmorpholine-*N*-oxide (NMO), afforded ketone **14** in 78% overall yield. Treatment of **14** with EtSH and $Zn(OTf)_2$ (CH_2Cl_2, rt) effected removal of the TES and benzylidene acetal groups with concomitant formation of a mixed thioketal. The resultant diol was reprotected as the acetonide to give **15** in 96% yield for the two steps. Finally, desulfurization under radical conditions[19] proceeded smoothly to give the BCD ring system **9** in 78% yield. The stereostructure of **9** was unambiguously confirmed by NOE analysis and coupling constants ($J_{11,12}$ = 9.2 Hz, $J_{14,15}$ = 9.0 Hz).

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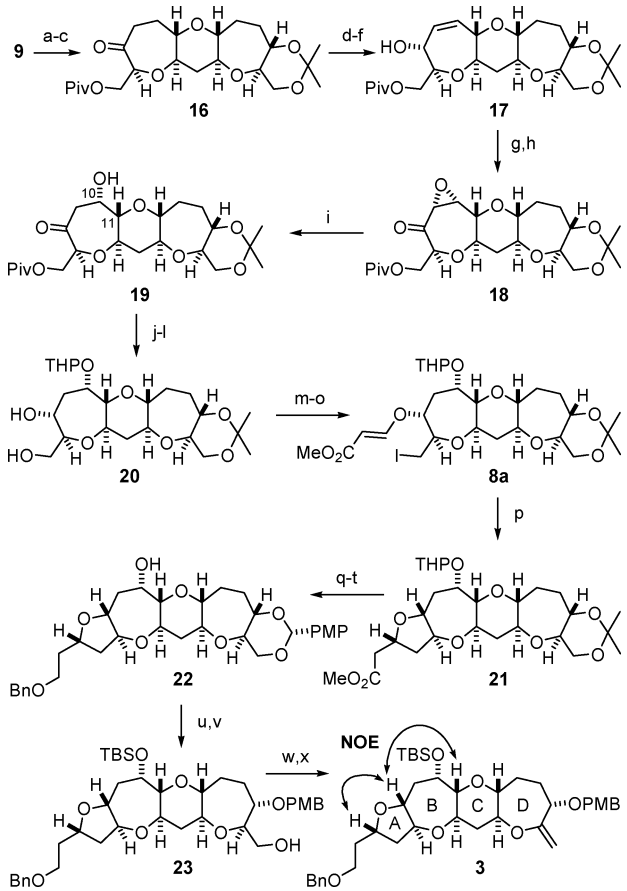
Scheme 4 [a]



[a] Reagents and conditions: (a) LDBB, THF, −78 °C; (b) PivCl, pyridine, CH_2Cl_2, rt, 90% (two steps); (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 81%; (d) LHMDS, TMSCl, Et_3N, THF, −78 °C; (e) $Pd(OAc)_2$, MeCN, rt, 96% (two steps); (f) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, rt, 88%; (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, rt, 83%; (h) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 81%; (i) Na[$PhSeB(OEt)_3$], HOAc, EtOH, 0 °C → rt, quant.; (j) DHP, CSA, CH_2Cl_2, rt; (k) L-Selectride, THF, −78 °C; (l) $LiAlH_4$, THF, 0 °C, 85% (three steps); (m) *p*-TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 81%; (n) methyl propiolate, *N*-methylmorpholine, CH_2Cl_2, 35 °C, 98%; (o) NaI, acetone, reflux, 74%; (p) *n*-Bu_3SnH, Et_3B, toluene, −78 °C, quant.; (q) $LiAlH_4$, THF, 0 °C; (r) KO*t*-Bu, BnBr, THF, rt; (s) CSA, MeOH, rt; (t) *p*-$MeOC_6H_4CH(OMe)_2$, 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.

With the BCD ring system in hand, we next turned to introduction of the C_{10} hydroxyl group (Scheme 4). Thus, reductive removal of the benzyl groups of **9** with lithium di-*tert*-butylbiphenylide (LDBB)[20] was followed by selective protection of the primary hydroxyl group as the pivalate ester (90% overall yield). The remaining secondary alcohol was then oxidized with TPAP/NMO to give ketone **16** in 81% yield. Conversion to the corresponding enone was achieved by formation of the silyl enol ether and ensuing oxidation with $Pd(OAc)_2$.[21] Subsequent treatment with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ (Luche reduction)[22] led to allylic alcohol **17** in 84% overall yield. Directed epoxidation[23] of **17** with *m*CPBA followed by oxidation of the secondary alcohol gave α,β-epoxy ketone **18** (67% yield for the two steps), which was then subjected to organoselenium-

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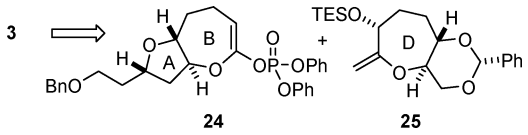
(22) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(23) For a review, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

Scheme 5. New Synthesis Plan for **3**

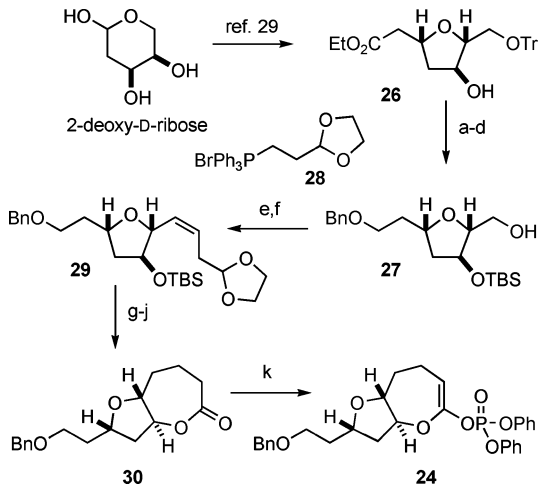


mediated reduction[24] to obtain the desired β-hydroxy ketone **19** in a quantitative yield as a single diastereomer. The stereochemistry of the C_{10} hydroxyl group was assigned by the small coupling constant, $J = 2.4$ Hz, between 10-H and 11-H. Protection of the hydroxyl group as the tetrahydropyranyl (THP) ether and stereoselective reduction of the ketone with L-Selectride, followed by reductive removal of the pivalate ester with $LiAlH_4$, afforded diol **20** in 85% yield for the three steps.

We next undertook the construction of the tetrahydrofuran ring A by an intramolecular radical cyclization of β-alkoxyacrylate.[25,26] Thus, selective tosylation of the primary hydroxyl group of **20** (81% yield) followed by reaction of the remaining secondary alcohol with methyl propiolate in the presence of *N*-methyl morpholine (NMM) gave β-alkoxyacrylate (Scheme 4). The tosylate was then displaced with sodium iodide (acetone, reflux) to afford a radical cyclization precursor, iodide **8a**, in 72% yield for the two steps. Treatment of **8a** with tributylstannane in the presence of triethylborane[27] in toluene at −78 °C effected cyclization of the tetrahydrofuran ring to deliver **21** in nearly quantitative yield. Tetrahydrofuranyl ester **21** was then converted into alcohol **22** in 71% overall yield through a four-step sequence, including ester reduction, benzylation of the resultant alcohol, acid hydrolysis of the acetal protective groups, and reprotection as its *p*-methoxybenzylidene acetal. Protection of the C_{10} alcohol as the *tert*-butyldimethylsilyl (TBS) ether followed by regioselective reductive cleavage of the *p*-methoxybenzylidene acetal with DIBALH[28] generated primary alcohol **23** in 88% overall yield. Synthesis of the ABCD ring exocyclic enol ether **3** was completed in 86% yield by a two-step sequence of iodination (I_2, PPh_3, imidazole) and base treatment (KO*t*-Bu, THF, 0 °C). The stereostructure of **3** was unambiguously confirmed by NOE analysis as shown.

The preceding entry to the ABCD ring fragment **3** was laborious, especially for the incorporation of the C_{10} alcohol, and therefore we decided to develop an alternative route with more convergency, as illustrated in Scheme 5. The second-generation synthesis commenced with the known alcohol **26**,[29] which was converted to primary alcohol **27** by straightforward protective and functional group manipulations (Scheme 6). Subsequent oxidation and Wittig reaction with the ylide derived from phosphonium salt **28** afforded cis-olefin **29** in 63% yield

Scheme 6 [a]



[a] Reagents and conditions: (a) TBSCl, imidazole, DMF, rt; (b) $LiAlH_4$, THF, 0 °C, 97% (two steps); (c) KO*t*-Bu, BnBr, THF, rt; (d) HCO_2H, Et_2O, 0 °C, 62% (two steps); (e) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C; (f) **28**, NaHMDS, THF, 0 °C, 63% (two steps); (g) H_2, Pd/C, EtOAc/MeOH, rt, 99%; (h) 1 M HCl, THF, 40 → 60 °C; (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, rt; (j) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C; DMAP, toluene, 110 °C, 79% (three steps); (k) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

for the two steps. Hydrogenation of the double bond and acid hydrolysis of the acetal and TBS groups, followed by oxidation of the resultant aldehyde with $NaClO_2$, gave a hydroxy acid. Lactonization by the Yamaguchi procedure[30] provided seven-membered lactone **30** (78% for the four steps), which was subsequently converted to enol phosphate **24** following the procedure of Nicolaou [KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C].[31]

Hydroboration of exocyclic enol ether **25**[16] with 9-BBN, followed by in situ reaction with **24**, afforded cross-coupled product **31** in 84% yield (Scheme 7). Subsequent hydroboration of enol ether **31** with thexylborane proceeded stereoselectively to yield alcohol (76%), which was oxidized with TPAP/NMO to give ketone **32** in 93% yield. For the stereoselective introduction of the C_{10} hydroxyl group, ketone **32** was converted to the corresponding silyl enol ether **33** (LHMDS, TMSCl, Et_3N, THF, −78 °C). Rubbotom-type oxidation of **33** with catalytic OsO_4 and NMO delivered α-hydroxy ketone **34** in 84% overall yield as an inseparable 8.5:1 mixture of diastereomers (vide infra).[32,33] After protection as the TIPS ether, the derived siloxy ketone **35** was separated as a pure form by silica gel chromatography. Unexpectedly, subsequent treatment of **35** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2 gave a mixture of hemiketal **36** (55%) and mixed thioketal **37** (29%). The hemiketal **36** was readily separated by column chromatography and resubjected to EtSH and $Zn(OTf)_2$ in 1:1 CH_2Cl_2/$MeNO_2$ to produce thioketal **37** in 95% yield. Thus, the desired **37** was obtained in 81% combined yield. In this transformation, direct treatment of ketone **35** with EtSH and $Zn(OTf)_2$ in 1:1 CH_2Cl_2/$MeNO_2$ resulted in a variable yield of **37** (0−61%). Following protection as the *p*-methoxy-

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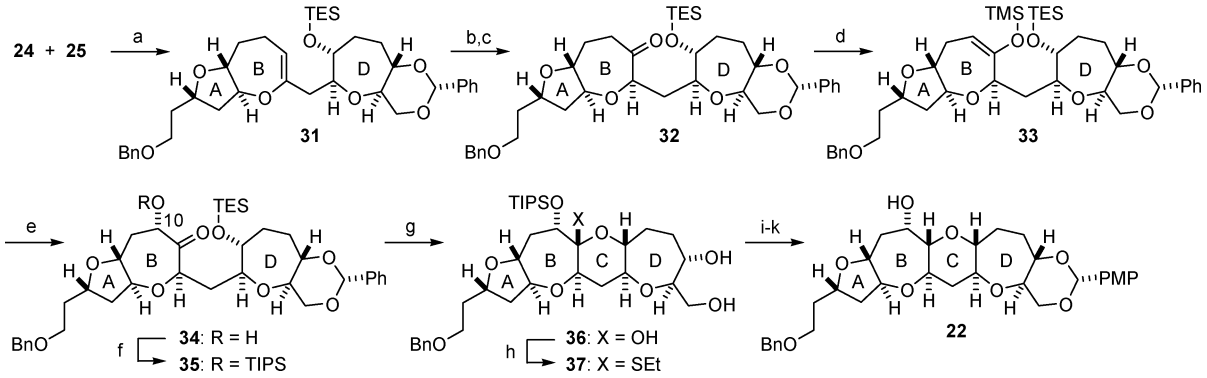
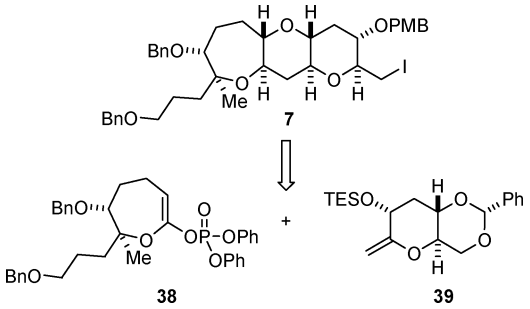
(27) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 2578.
(28) (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun*. **1984**, 201. (b) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.
(29) Matsuura, N.; Yashiki, Y.; Nakashima, S.; Maeda, M.; Sasaki, S. *Heterocycles* **1999**, *51*, 975.
(30) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989.
(31) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc*. **1997**, *119*, 5467.
(32) Product ratio was determined by ^{1}H NMR analysis (500 MHz) of the mixture.
(33) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett*. **1974**, *15*, 4319. (b) McCormik, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett*. **1981**, *22*, 607.

Scheme 7 [a]

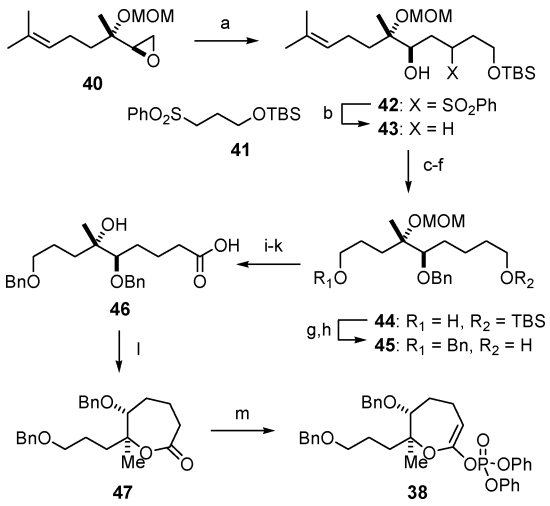


[a] Reagents and conditions: (a) **25**, 9-BBN, THF, rt; then 3 M aq Cs_2CO_3, **24**, $Pd(PPh_3)_4$, DMF, 50 °C, 84% from **30**; (b) $ThexylBH_2$, THF, 0 °C → rt; then aq NaOH, H_2O_2, rt, 76%; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 93%; (d) LHMDS, TMSCl, Et_3N, THF, −78 °C; (e) OsO_4, NMO, THF/H_2O, rt, 84% (two steps); (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 82%; (g) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, **36**, 55%; **37**, 29%; (h) EtSH, $Zn(OTf)_2$, 1:1 $MeNO_2/CH_2Cl_2$, rt, 95%; (i) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt; (j) Ph_3SnH, AIBN, toluene, 110 °C; (k) TBAF, THF, rt, 71% (three steps).

Scheme 8. Retrosynthesis Plan for Iodide **7**



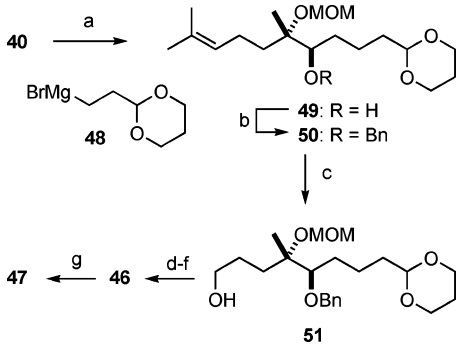
Scheme 9 [a]



[a] Reagents and conditions: (a) **41**, *n*-BuLi, THF/HMPA, −78 → 0 °C; **40**, 96%; (b) Na(Hg), Na_2HPO_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% (three steps); (l) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C; DMAP, toluene, 110 °C, 62%; (m) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

benzylidene acetal, the thioketal moiety was cleanly reduced under radical conditions to give, after desilylation, alcohol **22** (71% overall yield), which was then converged with the previous route (Scheme 4). This modified route to the ABCD ring fragment **3** required 33 steps over the longest linear sequence from 2-deoxy-D-ribose and proceeded with higher efficiency compared to the previous synthesis.

Scheme 10 [a]



[a] Reagents and conditions: (a) **48**, CuI, THF, −78 → 0 °C; (b) KO*t*-Bu, BnBr, THF, rt, 86% (two steps); (c) O_3, CH_2Cl_2, −78 °C; then $NaBH_4$, 90%; (d) KO*t*-Bu, BnBr, THF, rt; (e) 1 M HCl, THF, 70 °C; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 0 °C; (g) 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF, 0 °C; DMAP, toluene, 110 °C, 87% (four steps).

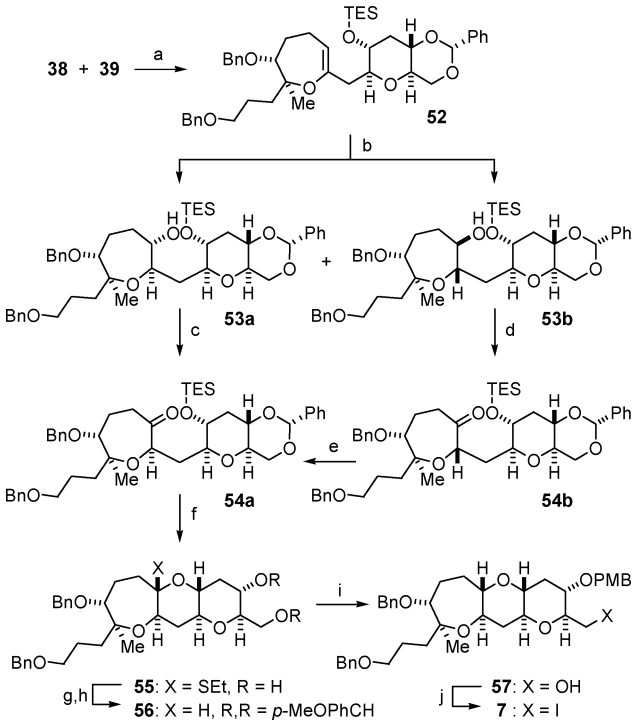
Synthesis of the Common Intermediate. The common intermediate **7** was envisioned to be constructed by a convergent union of monocyclic units **38** and **39** (Scheme 8). The synthesis of enol phosphate **38** commenced with the known epoxide **40**[34] derived from geraniol (Scheme 9). Reaction of **40** with the lithium anion generated from sulfone **41**[35] provided *β*-hydroxy sulfone **42** in 96% yield as a mixture of diastereomers. Subsequent treatment with excess amounts of sodium amalgam afforded alcohol **43** in 75% yield. After benzylation, successive osmium-catalyzed dihydroxylation, and periodate cleavage, followed by reduction with $NaBH_4$, provided primary alcohol **44** in 81% yield for the four steps. Benzylation and desilylation led to alcohol **45** (97% yield for the two steps), which was then converted to hydroxyl acid **46** by a two-step oxidation procedure followed by removal of the methoxymethyl (MOM) group with trifluoroacetic acid. Lactonization under the Yamaguchi conditions[30] provided seven-membered lactone **47** (62% yield), which was readily converted to the enol phosphate **38**.[31]

Although a synthetic route to **38** was secured, this procedure was not suitable for large-scale synthesis due to the use of excess

(34) Epoxide **40** 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. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

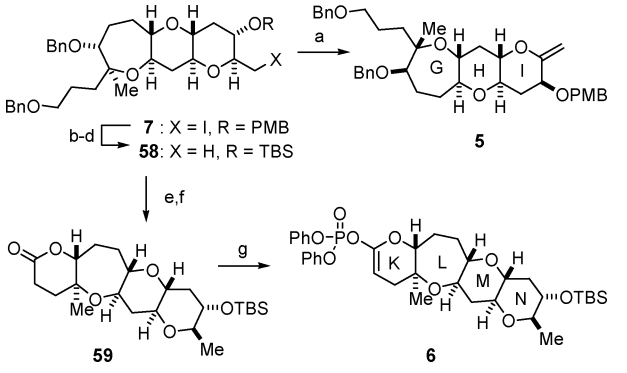
(35) Sulfone **41** was prepared from 1,3-propanediol in three steps and 77% overall yield: (i) TBSCl, Et_3N, CH_2Cl_2, rt; (ii) PhSSPh, *n*-Bu_3P, DMF, rt; and (iii) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C.

Scheme 11 [a]



[a] Reagents and conditions: (a) **39**, 9-BBN, THF, rt; then 3 M aq Cs_2CO_3, **38**, $PdCl_2$(dppf), DMF, 50 °C, 90% from **47**; (b) BH_3·SMe_2, THF, rt; then aq NaOH, H_2O_2, rt, **53a**, 42%; **53b**, 33%; (c) TPAP, NMO, 4 Å MS, MeCN, rt, 98%; (d) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 85%; (e) DBU, toluene, 110 °C, 51% (+ recovered ketone, 44%); (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, 74%; (g) *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt; (h) Ph_3SnH, AIBN, toluene, 100 °C; (i) DIBALH, CH_2Cl_2, −78 °C, 66% (three steps); (j) I_2, PPh_3, imidazole, benzene, rt, 89%.

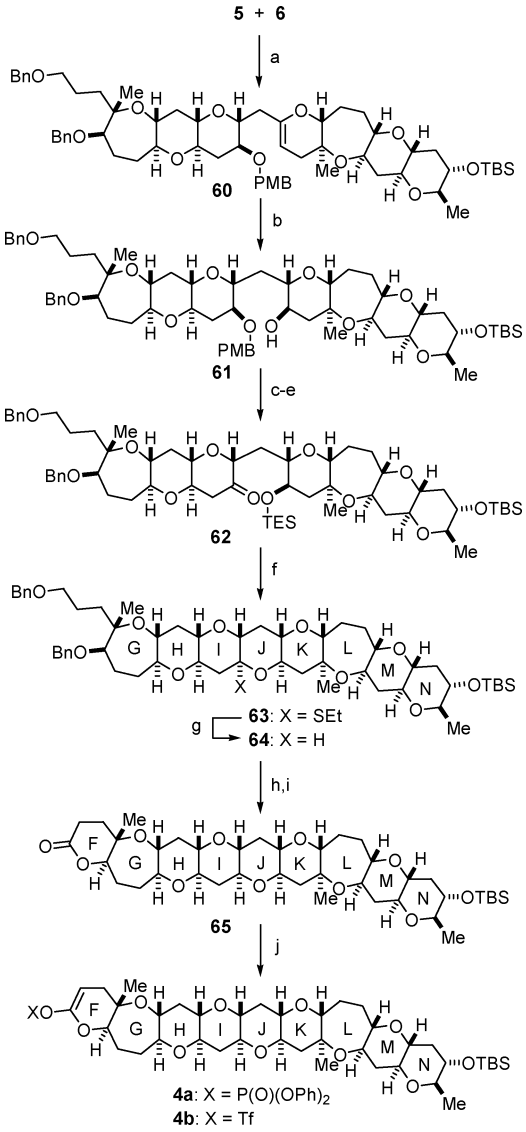
Scheme 12 [a]



[a] Reagents and conditions: (a) KO*t*-Bu, THF, 0 °C, quant.; (b) *n*-Bu_3SnH, AIBN, toluene, 100 °C; (c) DDQ, CH_2Cl_2/pH 7 phosphate buffer, rt, 76% (two steps); (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 91%; (e) H_2, $Pd(OH)_2$/C, EtOAc/MeOH, rt; (f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 98% (two steps); (g) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C.

amounts of sodium amalgam in the reduction of sulfone **42**. Accordingly, an alternative route to **38** was investigated. Copper-catalyzed opening of **40** with Grignard reagent **48** provided alcohol **49**, which was protected as the benzyl ether to give **50** (Scheme 10). This procedure afforded large quantities of **50** in 86% yield for the two steps. Ozonolysis followed by reductive treatment with $NaBH_4$ provided alcohol **51** in 90% yield. Following benzylation, acid hydrolysis of the acetal protective groups and oxidation of the resultant aldehyde with $NaClO_2$ led to acid **46**, which was then lactonized to give **47** in 87% yield for the four steps. This sequence is five steps shorter

Scheme 13 [a]

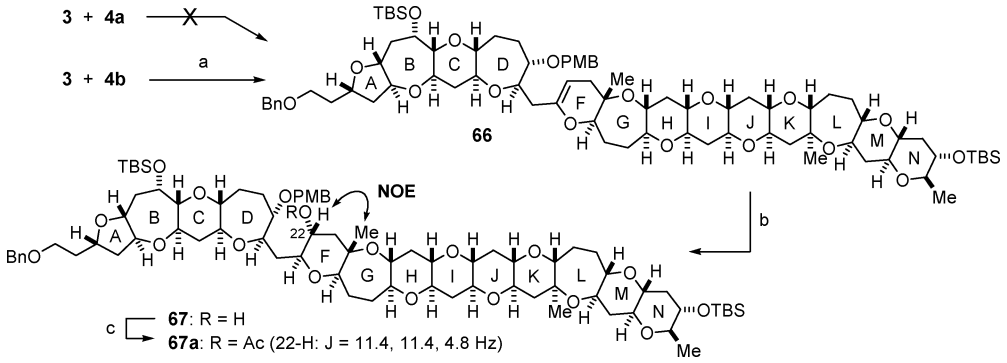


[a] Reagents and conditions: (a) **5**, 9-BBN, THF, rt; then 3 M aq Cs_2CO_3, **6**, $PdCl_2$(dppf)·CH_2Cl_2, DMF, 50 °C; (b) BH_3·THF, THF, −20 → 0 °C; then aq NaOH, H_2O_2, rt, 72% from **59**; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 81%; (d) DDQ, CH_2Cl_2/pH 7 phosphate buffer, rt, 90%; (e) TPAP, NMO, 4 Å MS, CH_2Cl_2, 86%; (f) EtSH, $Zn(OTf)_2$, CH_2Cl_2, rt, 87%; (g) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 92%; (h) H_2, $Pd(OH)_2$/C, EtOAc/MeOH, rt; (i) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, rt, 91% (two steps); (j) KHMDS, $(PhO)_2P(O)Cl$, THF/HMPA, −78 °C or KHMDS, Comins' reagent, −78 → 0 °C, 65% for **4a**; 80% for **4b**

overall and thus provided multigram quantities of **38** in eight steps from **40**.

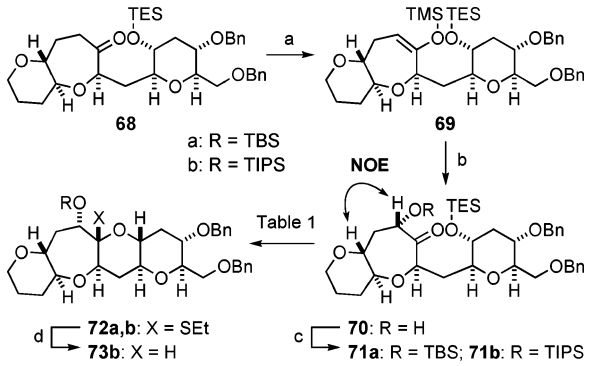
Hydroboration of exocyclic enol ether **39**[16] with 9-BBN and coupling with enol phosphate **38** delivered cross-coupled product **52** in 90% yield from lactone **47** (Scheme 11). Subsequent hydroboration produced a separable mixture of the desired alcohol **53a** (42%) and the corresponding diastereomer **53b** (33%). The observed poor stereoselectivity in this reaction is presumably due to the steric congestion of the pseudoaxial methyl group on the seven-membered ring. Oxidation of **53a** with TPAP/NMO provided ketone **54a** in excellent yield, whereas the undesired **53b** could be also converted to **54a**. Thus, **53b** was oxidized with TPAP/NMO to give ketone **54b** (85%), which upon treatment with DBU (toluene, 110 °C) afforded the thermodynamically favored **54a** and the starting material in 51

Scheme 14 [a]



[a] Reagents and conditions: (a) **3**, 9-BBN, THF, rt; then 3 M aq Cs_2CO_3, **4b**, $Pd(PPh_3)_4$, DMF, rt, 81%; (b) $BH_3{\cdot}SMe_2$, THF, 0 °C → rt; then aq NaOH, H_2O_2, rt, 75%; (c) Ac_2O, pyridine, rt.

Scheme 15 [a]



[a] Reagents and conditions: (a) LHMDS, TMSCl, Et_3N, THF, −78 °C; (b) OsO_4, NMO, THF/H_2O, rt, 99% (two steps); (c) TBSOTf or TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, **71a**, 54%; **71b**, quant.; (d) Ph_3SnH, AIBN, toluene, 110 °C, quant.

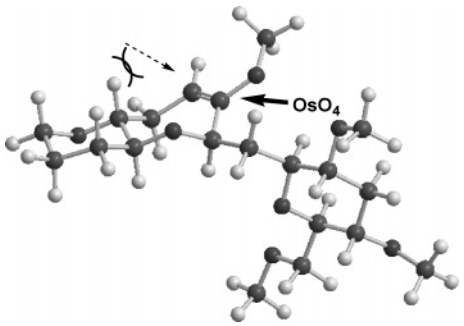


Figure 2. Rationalization of stereoselective osmylation.

Table 1. Fused Thioketalization

entry	compound	conditions	% yield
1	**71a** (R= TBS)	EtSH, $Zn(OTF)_2$	17
2	**71a** (R= TBS)	EtSH, $Zn(OTF)_2$, $NaHCO_3$	60
3	**71b** (R= TIPS)	EtSH, $Zn(OTF)_2$	81

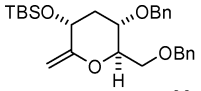
and 44% yield, respectively. The recovered **54b** was resubmitted to the reaction conditions to give **54a** in 79% combined yield after two recycles. The obtained ketone **54a** was subjected to EtSH and $Zn(OTf)_2$ to generate mixed thioketal **55** in 74% yield. Following reprotection as the *p*-methoxybenzylidene acetal, the thioketal moiety was cleanly reduced under radical conditions to give tricyclic ether **56** as the sole product. Regioselective reductive opening of the *p*-methoxybenzylidene acetal with DIBALH[28] afforded primary alcohol **57** (66% for the three steps), which was iodinated to furnish the common intermediate **7** in 89% yield.[36]

Synthesis of the FGHIJKLMN Ring Fragment. With the requisite **7** in hand, we turned to investigate its conversion to the GHI and KLMN ring fragments and their union to form the FGHIJKLMN ring fragment. Treatment of iodide **7** with potassium *t*-butoxide delivered the GHI ring exocyclic enol ether **5** in high yield (Scheme 12). On the other hand, radical reduction of **7** followed by replacement of the PMB with a TBS group afforded **58** in 69% overall yield. The benzyl groups were removed by hydrogenolysis, and the resultant 1,5-diol was oxidized with catalytic 2,2,6,6,-tetramethylpiperidinyloxy (TEMPO) and $PhI(OAc)_2$[37] to give lactone **59** (98% over the two steps), which was subsequently converted to the KLMN ring enol phosphate **6**.[31]

Hydroboration of **5** with 9-BBN followed by reaction with **6** in the presence of aqueous Cs_2CO_3 and $PdCl_2(dppf){\cdot}CH_2Cl_2$ (DMF, 50 °C) proceeded smoothly to give cross-coupled product **60** (Scheme 13). Subsequent hydroboration led stereoselectively to alcohol **61** in 72% yield from lactone **59**. Conversion to ketone **62** was accomplished in a three-step sequence of protection as its TES ether, removal of the PMB group, and oxidation of the resultant alcohol. The ensuing mixed thioketal formation and radical reduction furnished octacyclic polyether **64** in high yield. Hydrogenolysis of the benzyl groups and oxidation of the resultant diol with catalytic TEMPO and $PhI(OAc)_2$[37] provided nonacyclic lactone **65** (91% yield for the two steps), which was readily converted to the enol phosphate **4a** in 65% yield.[31] The corresponding enol triflate **4b** was also prepared in 80% yield from **65** by use of Comins' reagent[38] (KHMDS, Comins' reagent, THF/HMPA, −78 → 0 °C).

Construction of the Polycyclic Ether Skeleton. With the requisite key fragments **3** and **4** in hand, we investigated their crucial coupling using the Suzuki−Miyaura reaction. However, enol phosphate **4a** proved to be a poor substrate for this complex fragment coupling. Hydroboration of **3** and attempted coupling

(36) The present synthetic entry to iodide **7** is two step shorter than an earlier synthesis that used **39a** as an exocyclic enol ether coupling partner in the Suzuki−Miyaura coupling.[15a]

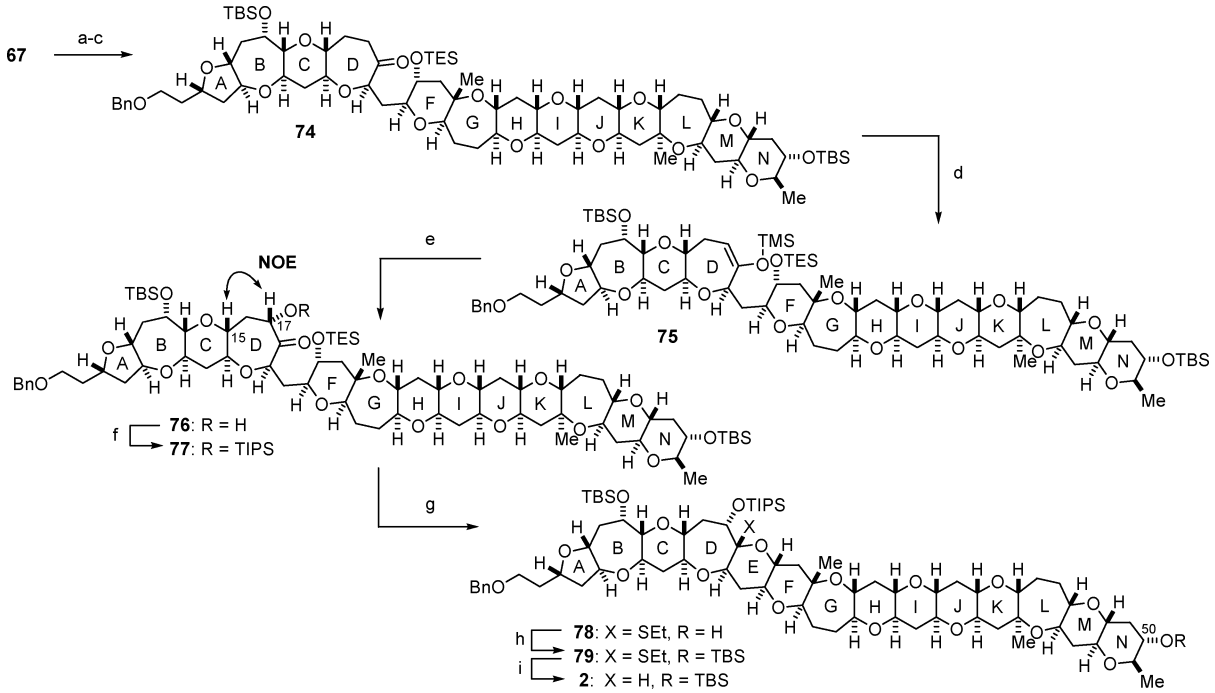


39a

(37) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57.

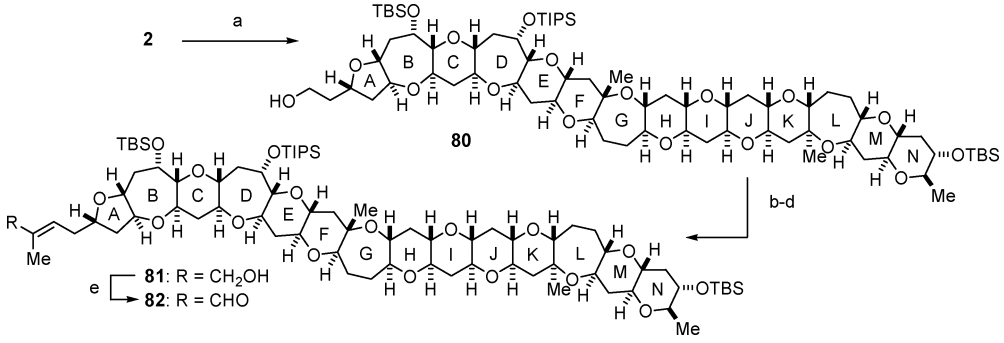
(38) Comins, D. L.; Dehghani, A. *Tetrahedron Lett*. **1992**, *33*, 6299.

Scheme 16 [a]



[a] Reagents and conditions: (a) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (b) DDQ, CH_2Cl_2/pH 7 phosphate buffer, 0 °C, 79% (two steps); (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt, 95%; (d) LHMDS, TMSCl, Et_3N, THF, −78 °C; (e) OsO_4, NMO, THF/H_2O, rt; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt, 85% (three steps); (g) EtSH, $Zn(OTf)_2$, $MeNO_2$, 0 °C → rt, **78**, 40%; **79**, 38%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 71%; (i) Ph_3SnH, AIBN, toluene, 110 °C, 98%.

Scheme 17 [a]



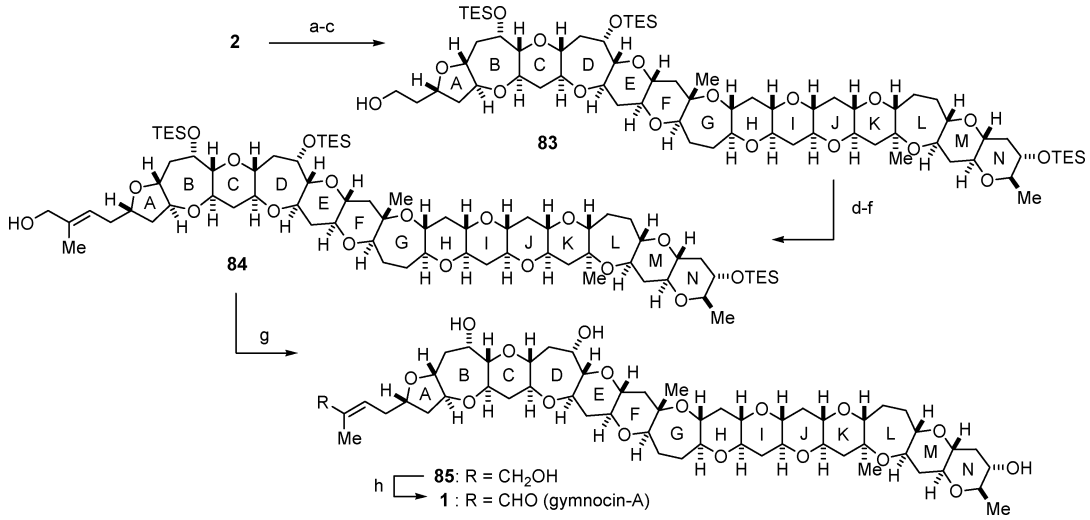
[a] Reagents and conditions: (a) LDBB, THF, −78 °C; (b) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (c) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, rt; (d) DIBALH, CH_2Cl_2, −78 °C, 77% (four steps); (e) MnO_2, CH_2Cl_2, rt, 75%.

with **4a** under the optimized conditions did not yield any desired product, and unreacted **4a** was recovered. After some experimentation, it was discovered that the pivotal fragment coupling could be realized by using more reactive enol triflate **4b**.[39] Thus, hydroboration of **3** with 9-BBN, followed by cross-coupling with **4b** in the presence of aqueous Cs_2CO_3 and $Pd(PPh_3)_4$ in DMF at room temperature, furnished the desired product **66** in excellent yield (81%) (Scheme 14). Considering the complexity and size of the fragments, this remarkable yield demonstrates the power and reliability of the Suzuki−Miyaura cross-coupling reaction. Coupled product **66** was then subjected to hydroboration ($BH_3{\cdot}SMe_2$; then H_2O_2, NaOH) to give alcohol **67** in 75% yield as a single stereoisomer. The stereochemistry at C_{22} was unambiguously determined by conversion into the corresponding acetate **67a** and its ^1H NMR coupling constant and NOE analysis as shown.

(39) Enol triflate was successfully used in a related coupling reaction: see ref 14e.

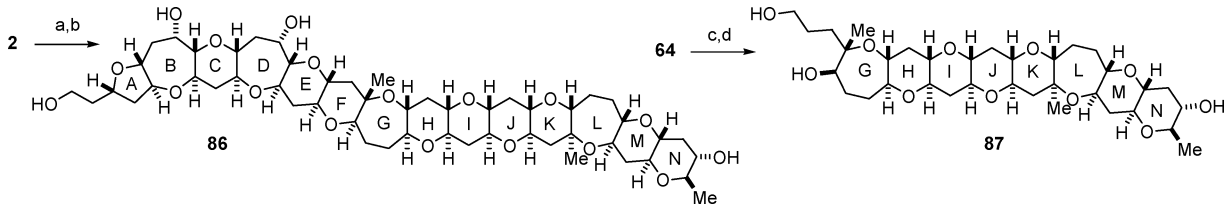
The next phase of our synthetic plan called for stereoselective introduction of the C_{17} hydroxyl group followed by ring closure of the E ring. To establish feasible conditions for these transformations, model studies were undertaken with compound **68**.[19] Stereoselective installation of the C_{17} alcohol was successfully accomplished by a Rubottom-type process (vide supra).[33] Thus, ketone **68** was converted to the corresponding silyl enol ether **69** (Scheme 15). Subsequent treatment with catalytic OsO_4 and NMO led exclusively to α-hydroxy ketone **70** in excellent yield. The stereochemistry at the newly generated hydroxy-bearing stereocenter was verified by NOE analysis as shown. The stereochemical outcome of the dihydroxylation of **69** can be rationalized by approach of OsO_4 onto the double bond from the less congested α-face in the most stable conformer, in which the opposite *β*-side was effectively blocked by an angular hydrogen (Figure 2). The ensuing mixed thioketal formation, however, turned out to be somewhat problematic. Treatment of TBS ether **71a** with EtSH and $Zn(OTf)_2$ in CH_2-

Scheme 18 [a]



[a] Reagents and conditions: (a) TBAF, 4 Å MS, MeCN/THF, 70 °C; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, rt; (c) LDBB, THF, −78 °C, 73% (three steps); (d) TPAP, NMO, 4 Å MS, CH_2Cl_2, rt; (e) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, rt; (f) DIBALH, CH_2Cl_2, −78 °C, 66% (three steps); (g) TAS-F, THF/DMF, 0 °C → rt; (h) MnO_2, $CHCl_3$, rt, 91% (two steps).

Scheme 19 [a]



[a] Reagents and conditions: (a) TBAF, 4 Å MS, MeCN/THF, 70 °C; (b) LDBB, THF, −78 °C, 67% (two steps); (c) TBAF, THF, rt; (d) H_2, $Pd(OH)_2$/C, EtOAc/MeOH, 97% (two steps).

Cl_2 resulted in a very poor yield (17%) of thioketal **72a**, presumably due to substrate decomposition resulting from cleavage of the TBS group (Table 1).[40] In fact, buffering the reaction mixture with $NaHCO_3$ improved the yield of **72a** (60%). Finally, the best result was obtained by exposure of TIPS ether **71b** to EtSH and $Zn(OTf)_2$ in CH_2Cl_2 to deliver mixed thioketal **72b** in 81% yield. Finally, radical reduction of **72b** afforded tetracyclic ether **73b** in high yield.

Application of this sequence to a more complex real system was highly successful (Scheme 16). Thus, alcohol **67** was converted to ketone **74** in 75% overall yield by a three-step sequence of protection as the TES ether, removal of the PMB group, and oxidation of the resultant alcohol. The ketone **74** was subsequently converted to the corresponding silyl enol ether **75** (LHMDS, TMSCl, Et_3N, THF, −78 °C). Upon oxidation with catalytic OsO_4 and NMO, the C_{17} hydroxyl group was installed with complete stereocontrol. The resultant alcohol **76** was then protected as its TIPS ether to provide **77** in high overall yield. The stereochemistry at the C_{17} position was verified by NOE between 15-H and 17-H on the ROESY spectrum.

The next task was to cyclize the E ring by radical reduction of mixed thioketal **79**. In sharp contrast to the analogous reaction with simple systems (cf. **62** → **63**, Scheme 13), treatment of ketone **77** with EtSH and $Zn(OTf)_2$ in CH_2Cl_2 resulted in only a poor yield of **79**. After some experimentation, it was found that the choice of solvent was critical for this process. The use of $MeNO_2$ as the solvent effected formation of mixed thioketal; however, some of the C_{50} TBS group was cleaved to yield a mixture of **78** (40%) and **79** (38%). Following separation, **78** was readily reprotected to give **79** in 71% yield. Finally, reductive desulfurization of **79** under radical conditions proceeded efficiently to furnish the tetradecacyclic polyether skeleton **2** in excellent yield, setting the stage for final elaboration to **1**.

Completion of the Total Synthesis. The last stage of the synthesis involved the incorporation of a 2-methyl-2-butenal side chain and global deprotection. Thus, the benzyl group of **2** was reductively removed with LDBB to give primary alcohol **80** (Scheme 17). Subsequent oxidation with TPAP/NMO followed by Wittig reaction using ethyl 2-(triphenylphosphoranylidene)propionate produced the corresponding enoate,[41] which was reduced with DIBALH to give allylic alcohol **81** in 77% yield for the four steps. Oxidation of **81** with MnO_2 furnished fully protected gymnocin-A (**82**) in 75% yield. However, preliminary attempts to remove the TBS and TIPS protective groups of **82** under various conditions, including tetra-*n*-butylammonium fluoride (TBAF), HF·pyridine. or tris(dimethylamino)sulfonium difluorosilicate (TAS-F),[42] led to decomposition of the starting material, presumably due to the labile nature of the enal-containing side chain. Global deprotection of allylic alcohol **81** was also unsuccessful. Prolonged and harsh

(40) Some byproducts were isolated, but their structures were not completely determined.

(41) Wittig reaction with 2-(triphenylphosphoranylidene)propionaldehyde (toluene, 80 °C) gave a poor yield of enal **82**.

(42) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

conditions required for removal of the TBS and TIPS ethers (e.g., TBAF, THF, 70 °C) led to decomposition, presumably resulting from competitive degradation of the allylic alcohol moiety.

Accordingly, we turned our attention to an alternative route, in which the TBS and TIPS groups were replaced with more readily cleaved TES ethers. Removal of the TBS and TIPS groups of **2** necessitated forcing conditions (excess TBAF, 4 Å molecular sieve, MeCN/THF, 70 °C, 12 h), but the deprotection proceeded cleanly to produce the corresponding triol. Subsequent reprotection as the TES ethers (TESOTf, 2,6-lutidine) followed by reductive removal of the benzyl group with LDBB led to primary alcohol **83** in good overall yield (Scheme 18). Oxidation to the corresponding aldehyde with TPAP/NMO followed by Wittig reaction with methyl 2-(triphenylphosphoranylidene)propionate produced the corresponding enoate, which was reduced with DIBALH to generate allylic alcohol **84** in 66% yield for the three steps. Global deprotection of the TES groups was successfully accomplished by means of TAS-F in THF/DMF (0 °C → rt) to deliver tetraol **85**.[43] Finally, chemoselective oxidation of the allylic alcohol moiety with MnO_2 completed the synthesis of gymnocin-A (**1**) in 91% yield for the two steps. The synthetic gymnocin-A was identical to the natural sample by ^1H and ^{13}C NMR and mass spectra, thus confirming the structure of gymnocin-A. Moreover, cytotoxic activity of synthetic gymnocin-A against P388 murine leukemia cells proved to be equipotent to that of the natural sample.

Synthesis and Evaluation of Analogues. The synthetic entry to gymnocin-A has thus allowed the generation of a diverse set of structural analogues not accessible by chemical modification of the natural product itself. To explore the structure−activity relationship profile of gymnocin-A, preliminary cytotoxicity studies were performed with some compounds, which were prepared from synthetic intermediates (Scheme 19). Compound **86**, lacking the enal side chain, was synthesized in 67% yield from advanced key intermediate **2** by successive deprotection of the silyl groups and benzyl ether removal. Truncated analogue **87** was obtained in 97% overall yield from **64** by global deprotection.

Cytotoxic activity of these compounds (**86** and **87**) and allylic alcohol **85** was measured against P388 murine leukemia cell line using the XTT assay.[44] As presented in Table 2, all these compounds showed no detectable inhibitory activity against P388, even at a concentration of 50 μg mL^{-1}. These results suggest that an electrophilic enal functionality of the side chain is important for exhibiting potent cytotoxic activity.

Table 2. Cytotoxicity (IC_{50} Value) of Gymnocin-A (**1**) and Analogues (**85**−**87**) against P388 Murine Luekemia Cells

compound	IC_{50} value (μg/mL)
1	1.3
85	>50
86	>50
87	>50

Conclusion

We have accomplished the first total synthesis of gymnocin-A, a marine polycyclic ether with the largest number of contiguous ether rings, through a highly convergent strategy. The synthesis heavily relied on our developed *B*-alkyl Suzuki−Miyaura coupling-based strategy, which undoubtedly is an important and general fragment coupling process in polycyclic ether synthesis. The present convergent synthesis of gymnocin-A employing three fragments of comparable complexity (**3**, **5**, and **6**) is well-suited for preparation of a diverse set of structural analogues of gymnocin-A to pursue the structure−activity relationship studies. Further extension of this chemistry along these lines is in progress and will be reported in due course.

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Supporting Information Available: Synthetic schemes for compounds **10**, **25**, **39**, and **68**, experimental procedures and spectral data for all new compounds, and comparison data for natural and synthetic gymnocin-A. This material is available free of charge via the Internet at http://pubs.acs.org.

JA042686R

(43) Treatment of **84** with TBAF (THF, rt) led to unidentified byproducts resulting from competitive decomposition of the allylic alcohol moiety.

(44) Scudiero, D. A.; Shoemaker, R. H.; Paull, K. D.; Monks, A.; Tierney, S.; Nofziger, T. H.; Currens, M. J.; Seniff, D.; Boyd, M. R. *Cancer Res.* **1988**, *48*, 4827.