Total Synthesis of Marine Polycyclic Ethers

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1. Introduction

In 1981, brevetoxin-B (BTX-B, **1**) was first isolated from the red tide organism *Gymnodinium breve*, and the unprecedented structure was disclosed by the Lin, Clardy, and Nakanishi groups.[1] The characteristic structural features include a unique trans-fused polycyclic ether ring system including 6-, 7-, and 8-membred cyclic ethers with 23 chiral centers. The biological activity is exerted by activating sodium channels and causing repetitive firing in neurons. Further efforts for isolation and structure elucidation of this family revealed many types of marine polycyclic ethers, which include brevetoxin-A (BTX-A, **2**), hemibrevetoxin-B (HBTX-B, **3**), ciguatoxins (CTX, **4**; CTX3C, **5**), gambierol (**6**), gymnocin-A (**7**), and so on (Figure 1).[2] These natural products also exhibit potent biological activities such as neurotoxicity, cytotoxicity, and antiviral and antifungal activities. One of the most exciting reports in this family is the isolation and structure determination of maitotoxin (MTX, **8**) from the dinoflagellate *Gambierdiscus toxicus*, by Murata, Yasumoto, and co-workers.[3,4] The unusual giant structure of MTX involves 32 fused ether rings containing 98 chiral centers, 28 hydroxyl groups, 21 methyl groups, and 2 sulfate esters. MTX is the most toxic and largest natural product (MW 3422) known to date, except for biopolymers.

The skeletal novelty, complexity, and biological activity of these marine polycyclic ethers have attracted much attention of chemists and biochemists. Thus, numerous synthetic chemists have extensively studied the development of new strategies and efficient methodologies for the construction of polycyclic ether ring systems and their application to the total synthesis of marine polycyclic ethers. After having completed the first total synthesis of HBTX-B (**3**) as the smallest marine polycyclic ether,[5] the Nicolaou group accomplished the first total syntheses of BTX-B (**1**)[6] and BTX-A (**2**)[7] as the large marine polycyclic ethers in 1995 and 1998, respectively, based on their developed effective strategies. Furthermore, during 2001−2005, recent remarkable progress has completed the total syntheses of several large marine

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Tadashi Nakata was born in Hokkaido, Japan, in 1943. He completed his B.S. and M.S. at the Faculty of Pharmaceutical Science, Hokkaido University, and joined RIKEN (The Institute of Physical and Chemical Research) at Wako as a researcher in 1969. After receiving his Ph.D. from Hokkaido University in 1974, he did his postdoctoral work at Harvard University with Prof. Y. Kishi (1976–1978). At RIKEN, he was promoted to Senior Researcher in 1985 and to Chief Scientist in 1992, and he retired in 2004. In addition, he joined Saitama University as a visiting associate professor (1989–1992) and a visiting professor (1992–2003). Since 2003, he has been a Professor of Chemistry at Tokyo University of Science. He received the PSJ (Pharmaceutical Society of Japan) Award for young scientist in 1985 and the PSJ Award in 2001. His research interests include development of useful synthetic methods and efficient synthetic strategies, total synthesis of complex natural products, and design of bioactive molecules.

polycyclic ethers by other groups: ciguatoxin CTX3C (**5**) by the Hirama group,[8] gambierol (**6**) by the Sasaki,[9] Kadota−Yamamoto,[10] and Rainier[11] groups, independently, BTX-B (**1**) by the Nakata group,[12] and gymnocin-A (**7**) by the Sasaki group.[13] The topics of effective methods including iterative, convergent, and biomimetic strategies for the construction of polycyclic ether ring systems have been reviewed.[14] This review focuses on the total syntheses of marine polycyclic ethers reported so far.[15]

2. Total Synthesis of Hemibrevetoxin-B

In 1989, Shimizu et al. reported the isolation of a new type of marine polycyclic ether, HBTX-B (**3**), from *Gymnodinium breve*, having about half the molecular size of brevetoxins.[16] The structure consists of a trans-fused six-,six-,seven-,seven-membered tetracyclic ether core (ABCD-ring) containing 10 chiral centers, an α-vinyl aldehyde moiety, and a (*Z*)-diene side chain. Since its isolation as the smallest member of marine polycyclic ethers, synthetic efforts by numerous synthetic organic chemists have been focused on HBTX-B (**3**).

The first total synthesis of **3** was achieved by the Nicolaou group in 1992.[5] In 1995 and 1996, the Yamamoto[17] and Nakata[18] groups achieved the second and third total syntheses, respectively, and the formal total syntheses were reported by the Mori[19] and Rainier[20] groups in 1997 and 2000, respectively. Most total syntheses of HBTX-B (**3**) were based on a linear synthetic strategy, because **3** is a rather small polycyclic ether that has only four cyclic ether rings. Recently, the Holton[21] and Fujiwara−Murai[22] groups have completed total and formal total syntheses through a convergent strategy, respectively. The synthetic strategy of each group is outlined in Figure 2. The order of construction of each ether ring and side chain for the synthesis of **3** is described by number, reaction names, and starting materials.

2.1. Nicolaou's Total Synthesis

Since the first isolation and structure determination of BTX-B (**1**) in 1981, Nicolaou and co-workers have extensively worked toward the total synthesis of marine polycyclic ethers, especially focused on the synthesis of BTX-B (**1**). Soon after the isolation of HBTX-B (**3**) in 1989, Nicolaou et al. turned their attention to the total synthesis of HBTX-B (**3**) and achieved the first total synthesis of **3** in 1992.[5]

Nicolaou et al. developed general methods for the construction of cyclic ether ring systems by 6- or 7-*endo*-cyclization of hydroxy vinylepoxide[23] and by the hydroboration of cyclic enol ether derived from thiolactone.[24] These methods were successfully applied to the construction of the B-, C-, and D-ring systems of HBTX-B (**3**), respectively (Figure 2).

The total synthesis of **3** by Nicolaou et al. started with D-mannose pentaacetate (**9**) (Scheme 1). Treatment of **9** with allyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$−TMSOTf afforded **10**.[25] After functional group manipulation, the resulting alcohol **11** was converted to the A-ring **12** by *n*-Bu_3SnH reduction of the corresponding xantate. Protective group manipulation of **12** led to dibenzyl ether **13**, which was subjected to ozonolysis, Wittig reaction, and DIBAH reduction to afford allyl alcohol **14**. The Sharpless asymmetric epoxidation[26] (AE) of **14** stereoselectively afforded α-epoxide (98%), which was converted to vinylepoxide **15** by oxidation with SO_3·py-DMSO followed by Wittig methylenation. The B-ring was constructed by their developed 6-*endo*-cyclization of hydroxy vinylepoxide;[23] after removal of the TBS group in **15**, treatment with CSA stereoselectively effected 6-*endo*-cyclization to give the AB-ring **16** in 90% yield. Then, construction of the C- and D-ring systems was successfully achieved by their strategy: that is, hydroboration of cyclic enol ether derived from thiolactone.[24] The standard chain elongation of **16** provided ester **17**, which was easily converted to seven-membered lactone **18** via the Yamaguchi lactonization.[27] After thiolactonization (82%) of **18** by Lawesson's reagent,[28] introduction of alkyl chain was performed by treatment with a higher order cuprate **19** to give **20** (85%). The cyclic enol ether **20** was also prepared in one-step using Murai's protocol;[29] treatment of **18** with LiHMDS and $PhNTf_2$ provide cyclic enol triflate, which was treated with **19** to give **20** (75%). Hydroboration of **20** produced a ca. 4:1 mixture of the desired β-alcohol **21** and α-isomer. The β-alcohol **21** was converted to lactone **22** in straightforward steps including the Yamaguchi lactonization. The lactone **22** was again treated with Lawesson's reagent and then the alkylcuprate **19** to give cyclic enol ether **23**. Hydroboration followed by Swern oxidation afforded a mixture of ketone **24** and its epimer, which was epimerized to the desired **24** by DBU treatment. Introduction of a methyl group to the ketone **24** with MeMgBr in Et_2O afforded a 1:1 mixture of the desired β-methyl product **25** and its

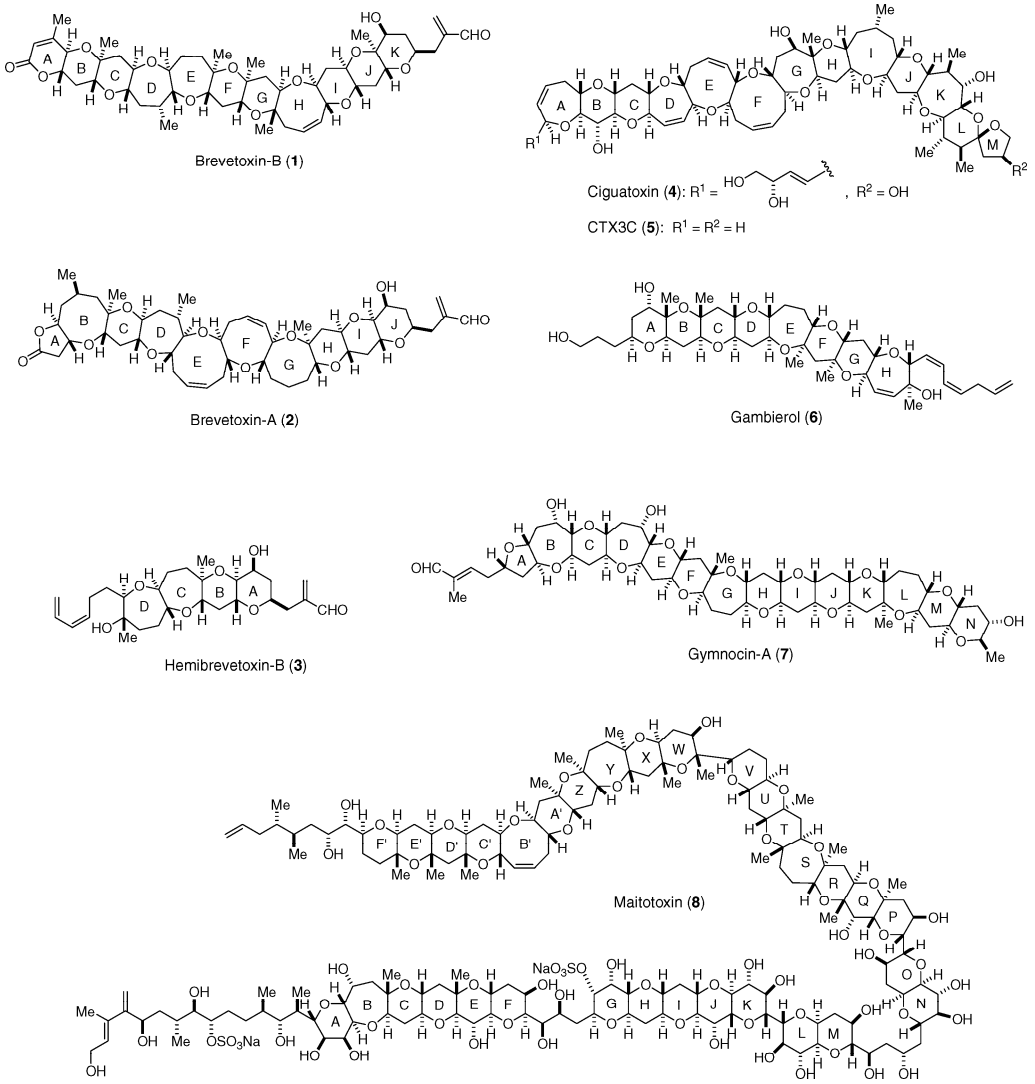


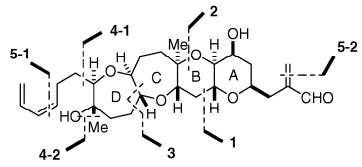
Figure 1. Structures of marine polycyclic ethers.

α-isomer. The ABCD-ring **25** was converted to ester **26** via chain elongation. After selective removal of the TBS group in **26** followed by Swern oxidation, introduction of the (*Z*)-diene unit as the side chain was effectively performed by Wittig reaction using $PhSe(CH_2)_2CH{=}PPh_3$ followed by H_2O_2 treatment to give **27**. Reduction of **27** with DIBAH followed by Swern oxidation provided aldehyde, which was treated with Eschenmoser's salt to give *exo*-methylene. Finally, removal of the TBS groups with SiF_4[30] furnished HBTX-B (**3**).

2.2. Yamamoto's Total Synthesis

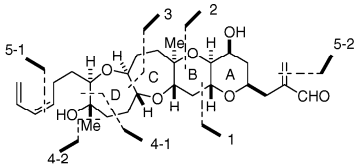
Yamamoto et al. developed Lewis acid (LA)-mediated intramolecular cyclization of γ-alkoxyallylstannane with aldehyde for the construction of tetrahydrofuran and tetrahydropyran rings.[31] The present method was successfully applied to the construction of the C- and D-ring systems of HBTX-B (**3**) (Figure 2).[17]

The AB-ring system **31** of HBTX-B (**3**) was first constructed by a modification of Nicolaou's route (Scheme 2).[23] The acetonide **28**, prepared from D-mannose pentaacetate (**9**), was transformed to allyl alcohol **29** by functional group manipulation. The Sharpless AE of **29**, oxidation with SO_3·py-DMSO, and Wittig reaction stereoselectively afforded α,β-unsaturated ester **30**. After removal of the TES group, treatment of **30** with CSA stereoselectively induced 6-*endo*-cyclization to give the AB-ring **31** in 81% yield, which was converted to allyl ether **32** in straightforward seven steps. Reaction of **32** with *s*-BuLi and *n*-Bu_3SnCl followed by SO_3·py oxidation afforded γ-alkoxyallylstannane **33**, which is a substrate for the intramolecular cyclization. Upon treatment of **33** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C, the cyclization stereoselectively took place to give the seven-membered C-ring **34** in 94% yield. After conversion of **34** to **35**, the diol **35** was effectively transformed to γ-alkoxyallylstannane **36** by a newly developed method via an acetal cleavage;[32] selective protection of the primary alcohol of **35** followed by treatment with $MeOCH{=}CHCH_2SnBu_3$ and CSA gave a mixed acetal, which was then treated with TMSI and HMDS to give γ-alkoxyallylstannane. Subsequent DIBAH reduction followed by SO_3·py oxidation led to aldehyde **36**, a substrate for the construction of the D-ring. Treatment of **36** with $BF_3{\cdot}Et_2O$ also stereoselectively induced an intramolecular cyclization to give the D-ring **37** in 98% yield. A



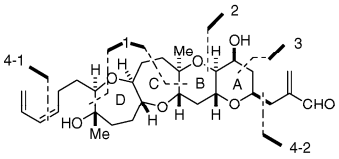
Nicolaou's strategy

1. A-ring: D-mannose pentaacetate, LA-mediated allylation
2. B-ring: *endo*-cyclization of vinylepoxide
3. C-ring: thiolactonization, alkylation, hydroboration
4. D-ring: thiolactonization, alkylation, Grignard methylation
5. Side chain: Wittig olefination, methylenation



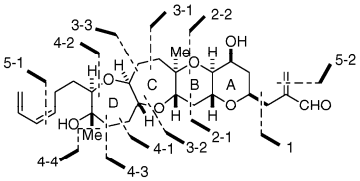
Yamamoto's strategy

1. A-ring: D-mannose pentaacetate, LA-mediated allylation
2. B-ring: *endo*-cyclization of vinylepoxide
3. C-ring: cyclization of γ-alkoxyallylstannane
4. D-ring: cyclization of γ-alkoxyallylstannane, Grignard methylation
5. Side chain: Wittig olefination, methylenation



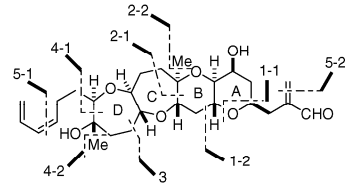
Nakata's strategy

1. C- and D-rings: geranyl acetate, double ring expansion
2. B-ring: *endo*-cyclization of styrylepoxide
3. A-ring: Grignard allylation, lactonization
4. Side chain: Wittig olefination, LA-mediated methallyllation



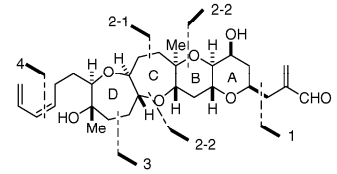
Mori's strategy

1. A-ring: tri-*O*-acetyl glucal, LA-mediated allylation
2. B-ring: oxiranyl anion addition, *endo*-cyclization
3. C-ring: oxiranyl anion addition, *endo*-cyclization, ring expansion
4. D-ring: oxiranyl anion addition, *endo*-cyclization, ring expansion Grignard methylation
5. Side chain: Wittig olefination, methylenation



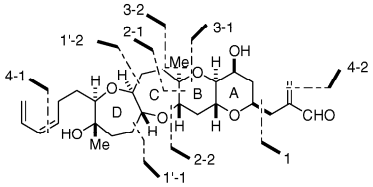
Rainier's strategy

1. A-ring: Diels–Alder reaction, LA-mediated allylation
2. B-ring: RCM, DMDO oxidn–methylation
3. C-ring: cyclic enol formation, DMDO oxidn–allylation
4. D-ring: RCM, DMDO oxidn–allylation, Grignard methylation
5. Side chain: Wittig olefination, methylenation



Holton's strategy

1. A-ring and side chain: tri-*O*-acetyl glucal, LA-mediated metacrylation
2. B- and C-rings: Pd-catalyzed coupling, cascade cyclization of hydroxy epoxide
3. D-ring: RCM
4. Side chain: Peterson olefination



Fujiwara–Murai's strategy

1. A-ring: tri-*O*-acetyl glucal, LA-mediated allylation
1') D-ring: RCM, lactone triflate, alkylation, hydroboration
2. C-ring: sulfoxide coupling, reductive cyclization of hydroxy ketone
3. B-ring: *S,O*-acetalization, methylation
4. Side chain: Wittig olefination, methylenation

Figure 2. Synthetic strategies for HBTX-B.

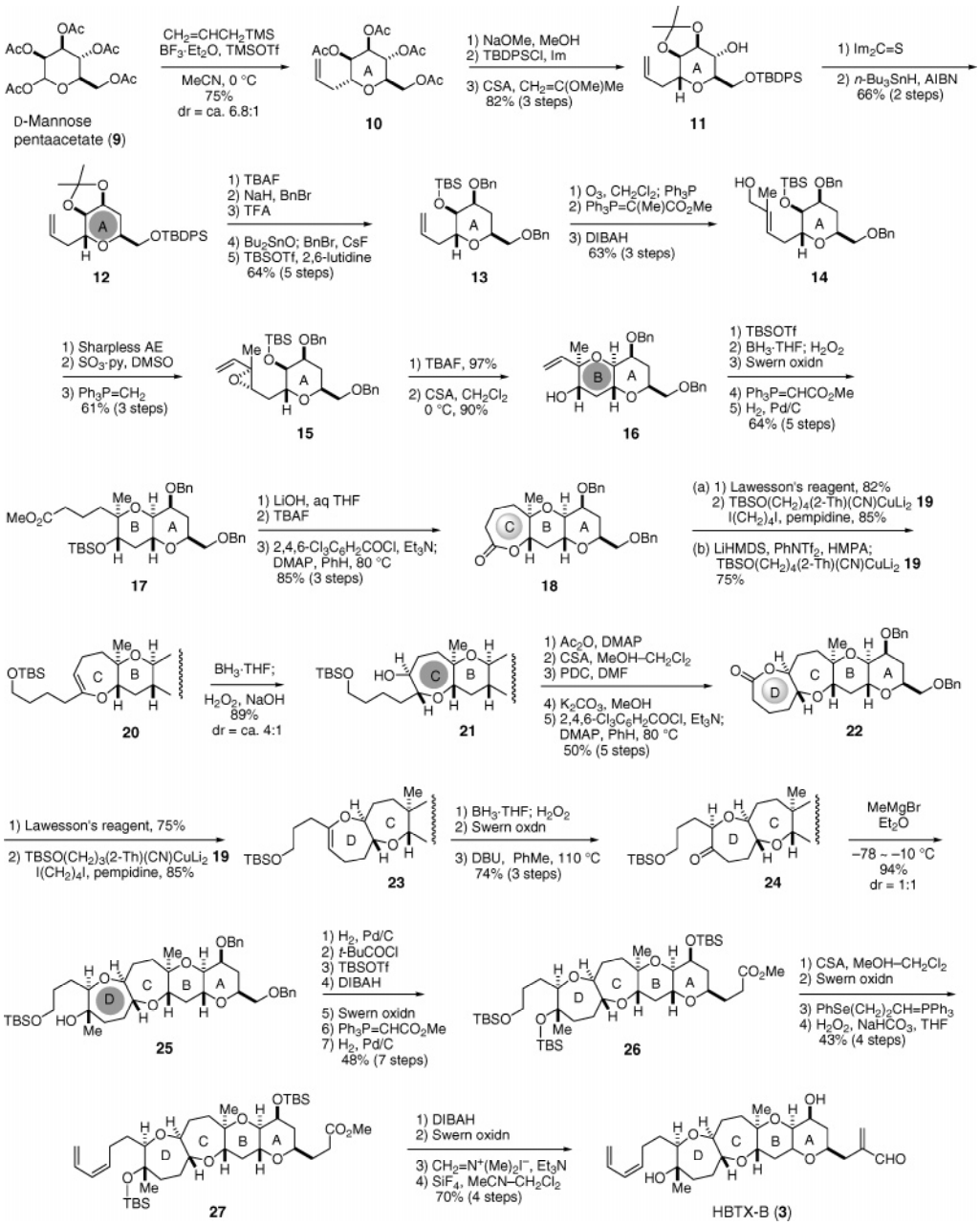
methyl group on the D-ring was then stereoselectively introduced. The Swern oxidation of **37** followed by methylation under Murai's conditions[33] (MeMgBr, toluene, −78 °C) afforded the desired β-methyl adduct **38** and its α-isomer in 83% yield with 86:14 diastereomeric ratio (dr). The chain elongation of **38** was then carried out to give alcohol **39** in five steps. The construction of (*Z*)-diene and α-vinyl aldehyde systems by following Nicolaou's procedure completed the total synthesis of HBTX-B (**3**).

2.3. Nakata's Total Synthesis

Nakata et al. developed a stereoselective ring expansion of five- or six-membered ethers with Zn(OAc)$_2$ to six- or seven-membered ethers, respectively.[34] The present method was efficiently applied to the construction of the seven-,seven-membered CD-ring system of HBTX-B (**3**) by double ring expansion of a six,six-membered bicyclic ether (Figure 2).[18]

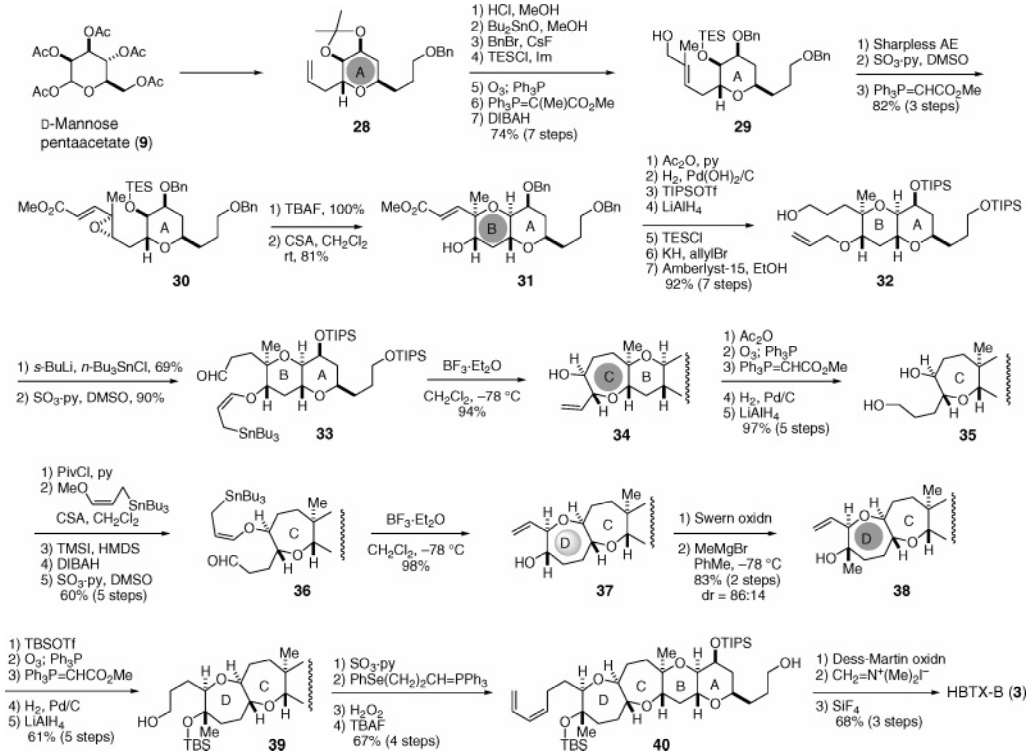
Allyl alcohol **41**, prepared from geranyl acetate, was converted to allyl alcohol **42** by Sharpless AE, regio- and stereoselective epoxide opening, and removal of the THP group (Scheme 3). Subsequent Sharpless AE of **42** afforded β-epoxide, which was treated with CSA to induce 6-*exo*-cyclization, giving tetrahydropyran **43**. Protection of the diol as the acetonide and chain elongation provided olefin **44**. The Wacker oxidation of **44** gave methyl ketone, which was subjected to the Horner−Wadsworth−Emmons (HWE) reaction, DIBAH reduction, and Sharpless AE to give α-epoxide **45**. After removal of the benzyl group, treatment of **45** with PPTS[35] also induced 6-*exo*-cyclization to give 6,6-bicyclic ether **46**. Epoxide formation followed by addition of allyl-MgCl

Scheme 1



in the presence of CuI afforded olefin **47**, which was converted to acetate **48** by hydrolysis of acetonide and acetylation. The CD-ring system, 7,7-bicyclic ether, was effectively constructed in one step from the 6,6-bicyclic ether using their developed ring expansion method.[34] After bismesylation of the diol **48** with $ClCH_2SO_2Cl$,[36] treatment of the resulting bis(monochloromesylate) **49** with $Zn(OAc)_2$ in aqueous AcOH at 60−80 °C effected double ring expansion to give 7,7-bicyclic ether **50**, corresponding to the CD ring, after methanolysis in 60% yield over three steps. Then, the triol **50** was converted to allyl alcohol **51** via chain elongation of the right side and protection of the left olefin as the diol acetonide. The construction of the B-ring was carried out by 6-*endo*-cyclization of hydroxy styrylepoxide,[37] which is a modified procedure of Nicolaou's method.[23] The Sharpless AE of **51** stereoselectively afforded α-epoxide, which was treated with TPAP−NMO[38] and then $Ph_3P{=}CHPh$ to give styryl epoxide **52**. After removal of the TMS group, treatment of **52** with CSA effected regio- and stereoselective 6-*endo*-cyclization to give the tetrahydropyran ring, which was acetylated to give the BCD-ring **53** in 71% yield over three steps. Subsequent TBS protection, ozonolysis, and Grignard reaction using allyl-MgBr afforded the desired β-alcohol **54** and α-alcohol in a 2:1 ratio. The isomeric α-alcohol was also converted to the same intermediate **56** in several steps. Ozonolysis of **54** followed by treatment with Dowex 50W−X2 in MeOH simultaneously induced acetal formation and removal of the acetonide to give diol, which was cleaved by $NaIO_4$ to aldehyde. The (*Z*)-diene system was then introduced by Nicolaou's procedure[5] using $PhSe(CH_2)_2CH{=}PPh_3$ to give **55**. The carbon four unit as the side chain was stereoselectively introduced in one step by treatment of **55** with $CH_2{=}C(CH_2OAc)CH_2TMS$ in the presence of TMSOTf to give TBS ether **56** (64%) and alcohol **57**

Scheme 2



(34%). To remove the TBS group, **56** was again treated with TMSOTf to give **57**. Finally, methanolysis of the acetate **57** followed by oxidation with MnO_2 furnished HBTX-B (**3**).

2.4. Mori's Formal Total Synthesis

Mori et al. developed an iterative strategy for the construction of polycyclic ethers based on coupling between sulfonyl-stabilized oxiranyl anion and triflate followed by *endo*-cyclization.[39] The strategy was effectively applied to the successive construction of the B-, C-, and D-ring systems of HBTX-B (**3**) (Figure 2).[19]

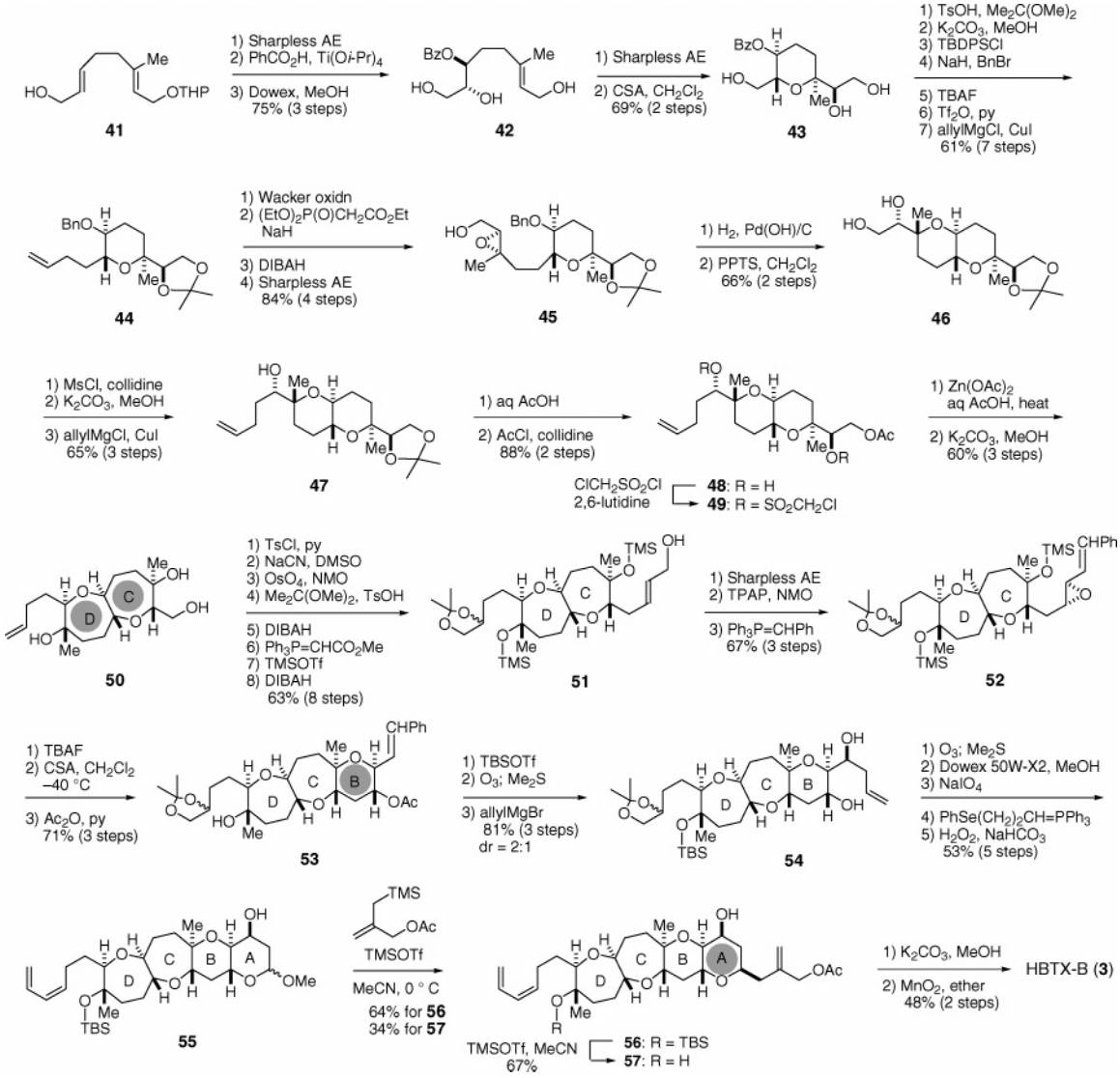
The A-ring system **60** was constructed starting from tri-*O*-acetyl-D-glucal (**58**) via **59** in nine steps (Scheme 4). The diol **60** was regioselectively activated and protected by their one-pot procedure (Tf_2O, 2,6-lutidine; then TESOTf) to give triflate **61**. Coupling of the triflate **61** and an oxiranyl anion, derived from epoxy sulfone **62** with *n*-BuLi, smoothly proceeded in THF−HMPA at −100 °C to give **63** in 98% yield. Treatment of **63** with TsOH effected 6-*endo*-cyclization to give 6,6-bicyclic ether **64** in 90% yield. Reduction of the ketone **64** with $NaBH_4$ stereoselectively afforded the desired α-alcohol (92%), which was converted to aldehyde **65** by protective and functional group manipulations. Coupling of **65** and epoxy sulfone **66** with *n*-BuLi afforded *β*-alcohol **67** (63%) and its epimeric α-alcohol (25%). Treatment of the *β*-alcohol **67** with $BF_3{\cdot}Et_2O$ induced its clean cyclization to tricyclic ketone **68** (76%), whereas the α-isomer did not cyclize under the same conditions. The seven-membered C-ring system was constructed by ring expansion using $TMSCHN_2$[40] as follows. SmI_2-induced reductive removal of the hydroxyl group in **68** (64%) and ring expansion with $TMSCHN_2-BF_3{\cdot}Et_2O$ followed by PPTS treatment provided the desired oxepane **69** in 67% yield. After desilylation of **69**, hydroxy-directed reduction with $Me_4NBH(OAc)_3$ gave the expected *β*-alcohol as a single product, which led to triflate **70** by one-pot triflation and TES protection. Reaction of **70** and epoxy sulfone **71** with *n*-BuLi afforded coupling product **72** in 96% yield. Subsequent removal of the TES group and $BF_3{\cdot}Et_2O$-promoted 6-*endo*-cyclization provided the desired ketone **73**. Ring expansion reaction using $TMSCHN_2$ was again applied to the construction of oxepane to give 6,6,7,7-tetracyclic ketone **74** (62%), which was treated under Murai's conditions[33] (MeMgBr, toluene) to give *β*-methyl adduct **75** (77%) and its α-epimer (21%). The protective group manipulation afforded Yamamoto's key intermediate **39**. Thus, the formal total synthesis of HBTX-B (**3**) was accomplished.

2.5. Rainier's Formal Total Synthesis

Rainier et al. developed a flexible and iterative *C*-glycoside strategy for the construction of polycyclic ethers based on epoxidation of cyclic enol ether, addition of *C*-nucleophile, and ring-closing olefin metathesis (RCM) or acid-mediated annulation.[41] The strategy was successfully applied to the construction of the B-, C-, and D-ring systems of HBTX-B (**3**) (Figure 2).[20]

The formal total synthesis of (±)-HBTX-B (**3**) by Rainier et al. started with a hetero-Diels−Alder addition for the construction of the A-ring (Scheme 5). Cycloaddition of Danishefsky's diene **76** with aldehyde **77** provided enone **78**, which was converted to alcohol **79** via Luche reduction,[42] *m*CPBA oxidation, and regioselective benzylation. Stereoselective allylation of **79** with allyl-TMS-TMSOTf afforded the

Scheme 3



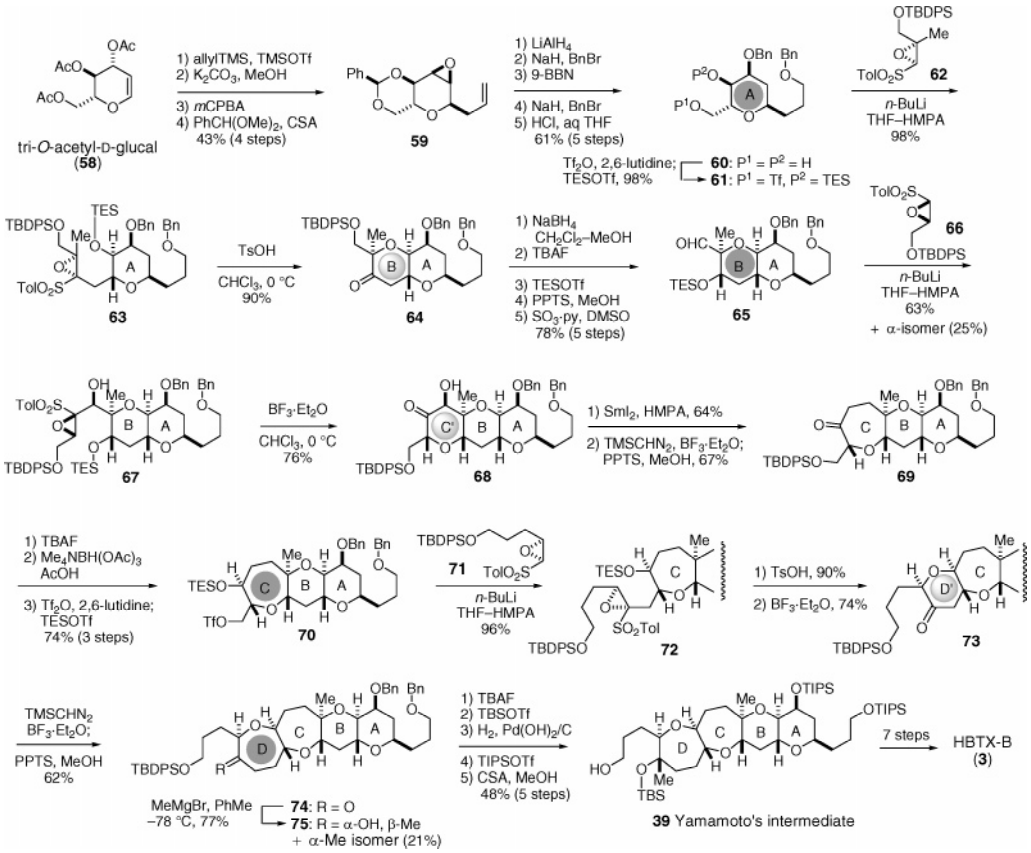
A-ring **80**, which was coupled with $(MeO)_2CH(CH_2)_3CO_2H$ to give ester **81**. Takai's protocol[43] provided a mixture of acyclic and cyclic enol ethers, which was treated with Schrock molybdenum catalyst **82**[44] to give cyclic enol ether **85** in 78% yield. Grubbs ruthenium catalyst **84**[45] was also effective for this cyclization to give **85** in 82% yield. Then, introduction of hydroxyl and methyl groups in the B-ring was accomplished by epoxidation of **85** with DMDO followed by treatment with Me_3Al to give the desired B-ring **86** in 75% yield with the correct stereochemistry. Treatment of **86** with PPTS afforded cyclic enol ether **87**, which was again subjected to their protocol. Epoxidation of **87** with DMDO followed by allyl-MgCl gave a single alcohol (64%), which was allylated to give allyl ether **88**. RCM of **88** with Grubbs catalyst **83**[46] followed by olefin isomerization using Wilkinson catalyst gave **89**. Subsequent DMDO epoxidation and allylation afforded the D-ring **90** (84%) as a 3:1:1 mixture of three isomers, after acetylation. Hydroboration of **90**, TBDPS protection, methanolysis, and Swern oxidation gave seven-membered ketones, which were treated with NaOEt to epimerize to (±)-**74**, which is the key intermediate in Mori's formal total synthesis.[19] Thus, formal total synthesis of (±)-HBTX-B (**3**) was accomplished.

2.6. Holton's Total Synthesis

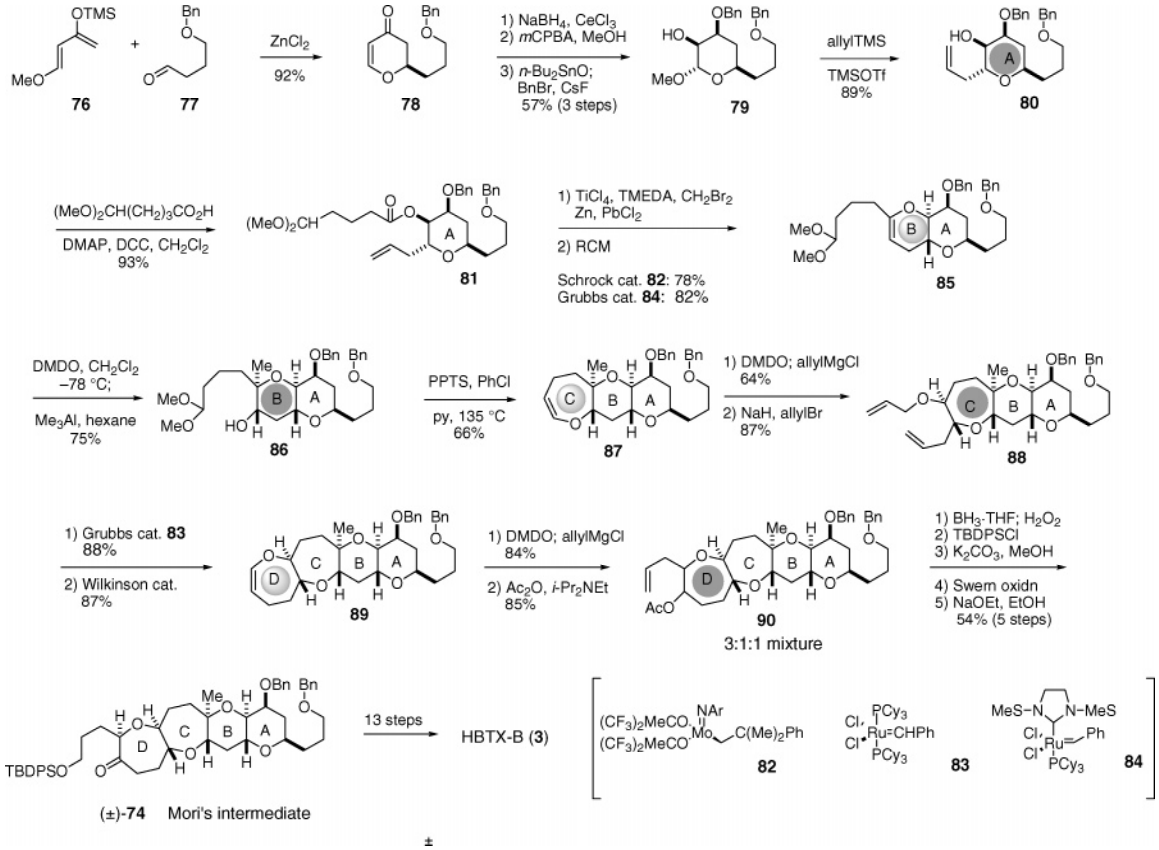
Holton et al. achieved the first convergent total synthesis of HBTX-B (**3**) based on a biomimetic and cascade cyclization of hydroxy epoxide for the construction of the B- and C-ring systems (Figure 2).[21] The precursor **104** for the cascade cyclization was synthesized by the union of two fragments **93** and **100**, corresponding to the C12−C21 and C1−C11 fragments, respectively (Scheme 6).

The synthesis of the iodide **93** started with diol **91**, which was prepared from benzyl β-D-arabinopyranoside (Scheme 6).[47] The diol **91** was converted to lactone **92** via coupling with *tert*-butyl bromoacetate. Allylation of **92** afforded β-allyl adduct (83%) and its α-diastereomer (5%). Oxidative cleavage of the double bond, $NaBH_3CN$ reduction, and iodination led to the desired iodide **93**. The synthesis of the other coupling partner **100** started with *C*-allylation of tri-*O*-acetyl-D-glucal (**58**). Treatment of **58** with 2-trimethylstannylacrylate (**94**) in the presence of $BF_3{\cdot}Et_2O$ afforded **95** (93%) and the C4 epimer (7%). Methanolysis of

Scheme 4

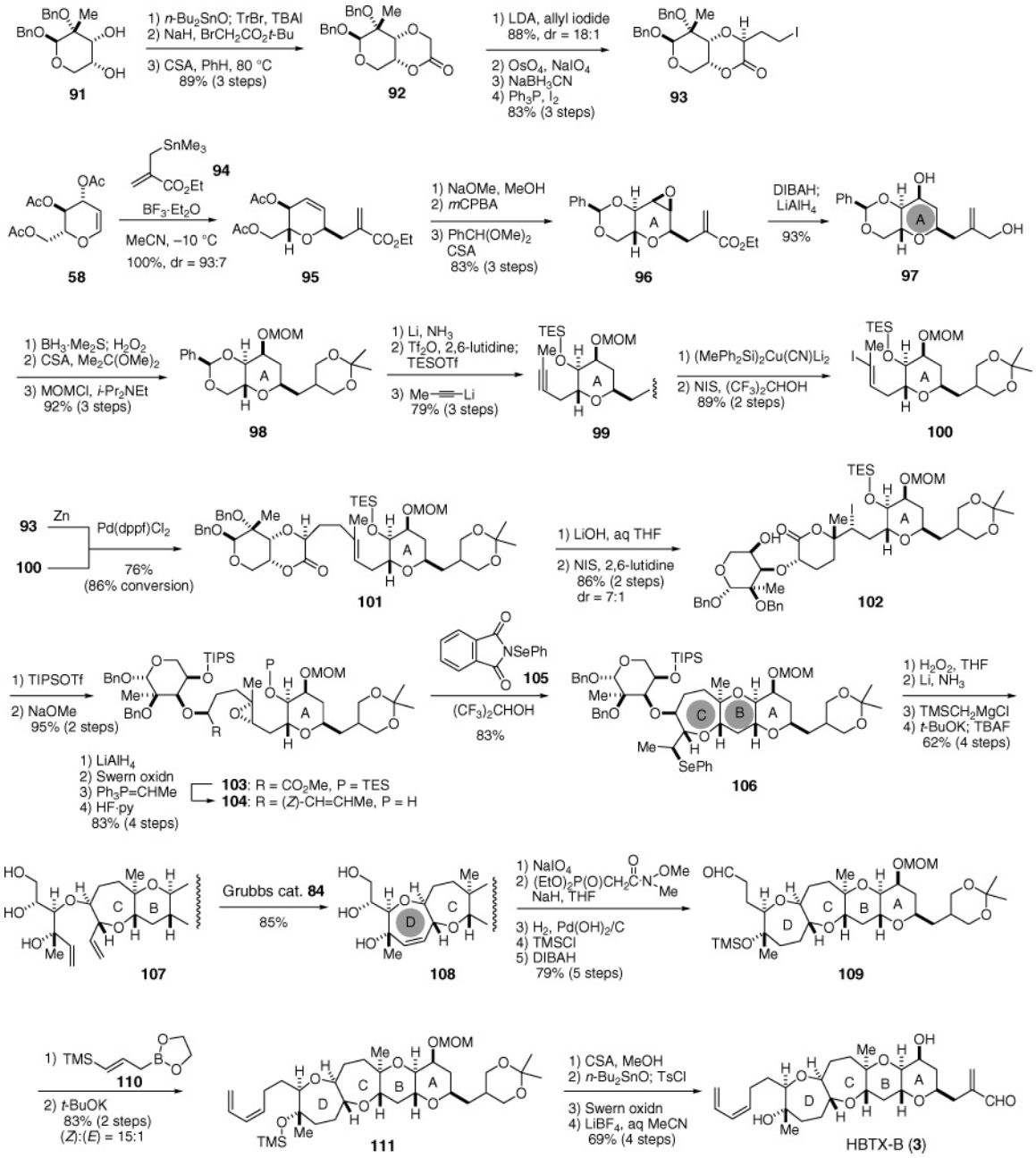


Scheme 5



the diacetate **95** followed by *m*CPBA oxidation stereoselectively afforded β-epoxide, which was protected as the benzylidene acetal **96**. One-pot treatment of **96** with DIBAH and $LiAlH_4$ reduced the epoxide and ester to give diol **97**. After hydroboration, the resulting triol was protected as the MOM-

Scheme 6

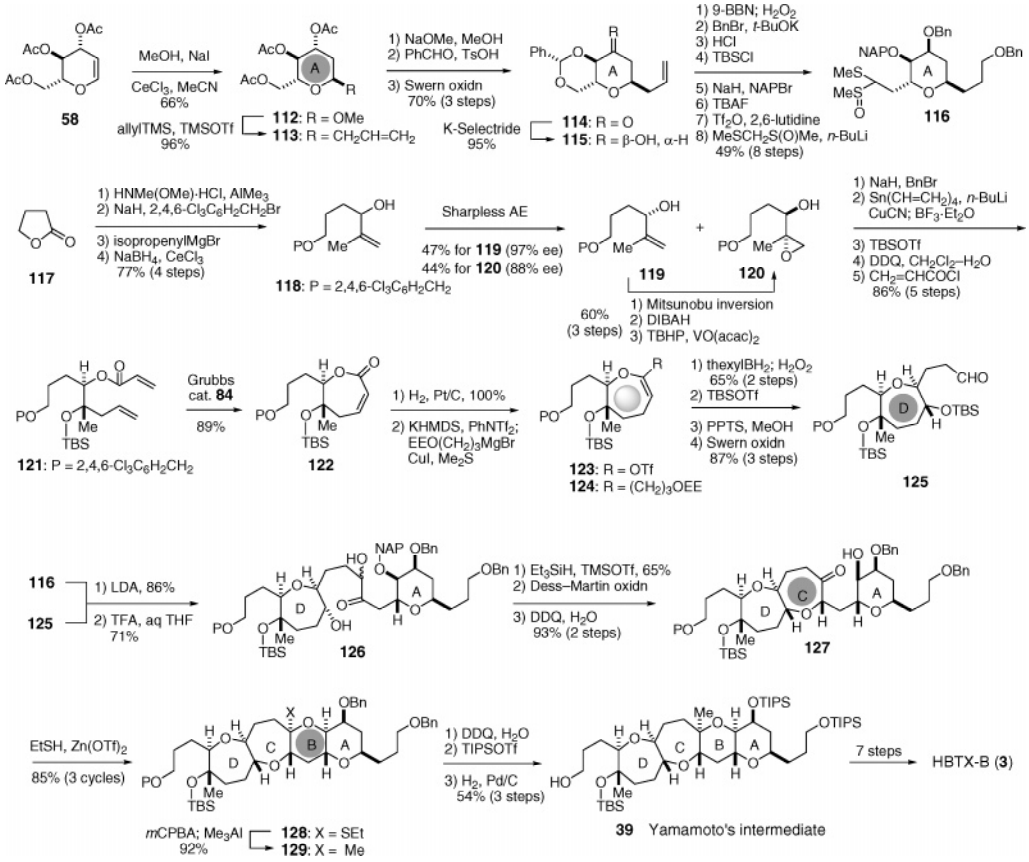


acetonide **98**. Deprotection of the benzylidene acetal followed by one-pot triflation−silylation afforded triflate, which was coupled with acetylide and subjected to iododesilylation with NIS in $(CF_3)_2CHOH$ to give the desired vinyl iodide **100** with complete retention of the olefin geometry.

The coupling of two segments **93** and **100** was accomplished by Pd(dppf)Cl_2-catalyzed reaction of organozinc iodide and vinyl iodide (Scheme 6).[48] The alkylzinc iodide, prepared from **93** using Rieke active zinc, was coupled with the vinyl iodide **100** to afford **101** in 76% yield. Hydrolysis of the lactone **101** followed by iodo-lactonization with NIS produced iodo-lactone **102** (75%) along with its diastereomer (11%). TIPS protection of **102** and methanolysis provided epoxy-ester **103**, which was converted to the key intermediate **104** for the cascade cyclization. The challenging cascade cyclization smoothly and stereoselectively proceeded in $(CF_3)_2CHOH$ with *N*-(phenylseleno)phthalimide **105** at 0 °C to give **106** in 83% yield.

The completion of the total synthesis was carried out via D-ring construction by RCM and introduction of the side chain. Oxidative elimination of the selenide **106**, removal of the benzyl group, and olefination afforded diene **107**. RCM of **107** with Grubbs catalyst **84** afforded the D-ring **108** in 85% yield, which was converted to aldehyde **109**. Insertion of (*Z*)-diene was stereoselectively accomplished by the Peterson procedure using **110**[49] to give **111** in 83% yield (*Z*/*E* = 15:1). Formation of α-vinyl aldehyde at the right side was performed by deprotection of the acetonide and TMS groups, selective tosylation, and Swern oxidation. Final removal of the MOM group with $LiBF_4$ furnished HBTX-B (**3**).

Scheme 7



2.7. Fujiwara–Murai's Formal Total Synthesis

The Fujiwara−Murai group developed a convergent strategy for the construction of cyclic ethers via coupling of dithioacetal mono-*S*-oxide, as an acyl anion equivalent, and aldehyde.[50] The strategy was successfully applied to the union of the A- and D-ring systems in their formal total synthesis of HBTX-B (**3**) (Figure 2).[22]

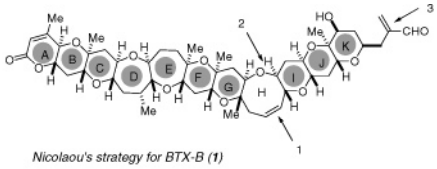
The A-ring **113** was synthesized from tri-*O*-acetyl glucal (**58**) by treatment with MeOH and NaI in the presence of $CeCl_3$ followed by allyl-TMS-TMSOTf (Scheme 7). Protective and functional group manipulations led to the desired dithioacetal mono-*S*-oxide **116** as a coupling partner. The synthesis of the D-ring started with γ-lactone **117**. The Sharpless AE for kinetic resolution of **118** afforded optically active alcohol **119** and epoxide **120**. The Mitsunobu inversion of the alcohol **119** followed by DIBAH reduction and Sharpless epoxidation led to the desired **120**. The epoxide **120** was converted to **121** via introduction of a vinyl group and acrylation. RCM of the ester **121** with Grubbs catalyst **84** afforded α,β-unsaturated lactone **122** in 89% yield. After hydrogenation, the lactone **122** was converted to cyclic enol ether **124** using Murai's method.[29] Subsequent functional group manipulation including stereoselective hydroboration led to the functionalized D-ring aldehyde **125**, as the other coupling partner.

The coupling of the A- and D-rings, **116** and **125**, was accomplished by their developed method.[50] Treatment of **116** with LDA followed by addition of the aldehyde **125** afforded the coupling product as a mixture of diastereomers, which was converted to dihydroxy ketone **126** by removal of the TBS and dithioacetal mono-*S*-oxide groups. The C- and B-rings were then constructed by following Nicolaou's protocols: (1) reductive cyclization of hydroxy ketone[51] and (2) *S*,*O*-acetal formation by hydroxy dithioacetal cyclization followed by reduction (or alkylation).[52] Reductive cyclization of **126** with $Et_3SiH-TMSOTf$ performed construction of the C-ring (65%), and subsequent Dess−Martin oxidation followed by removal of the NAP group afforded hydroxy ketone **127**. Treatment of **127** with $EtSH-Zn(OTf)_2$ effected intramolecular *S*,*O*-acetal formation to give **128**, which was successively treated with *m*CPBA and $AlMe_3$ to give the B-ring **129**, introducing an angular methyl group. Protective group manipulation provided Yamamoto's intermediate **39**, which completes the formal total synthesis of HBTX-B (**3**).

Besides the total syntheses of HBTX-B (**3**), the smallest marine polycyclic ether, total syntheses of other large marine polycyclic ethers such as BTXs, CTXs, gambierol, and gymnocins have been accomplished based on the convergent strategies. The strategies of each group toward the target molecules are outlined in Figure 3. The order of construction of each ether ring and the side chain in the key segments and final steps of total synthesis are described by number and reaction names.

3. Total Synthesis of Brevetoxin-B

BTX-B (**1**), produced by the red tide organism, *Gymnodinium breve* Davis, is the first and most

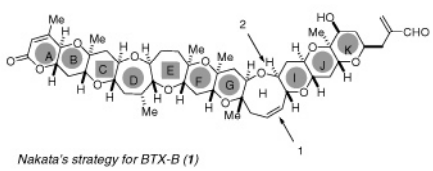


*Nicolaou's strategy for BTX-B (**1**)*

Synthesis of the ABCDEFG-ring
1. F-ring: 6-*endo*-cyclization of vinylepoxide
2. G-ring: 6-*endo*-cyclization of vinylepoxide
3. E-ring: lacotone enol triflate, cuprate addition, hydroboration
4. D-ring: lactone enol triflate, Cr(II)-Ni(II)-mediated coupling, hydroboration
5. C-ring: intramolecular Michael addition
6. B-ring: 6-*endo*-cyclization of vinylepoxide
7. A-ring: HWE-lactonization

Synthesis of the IJK-ring
1. K-ring: LA-mediated allylation
2. J-ring: intramolecular Michael addition
3. I-ring : 6-*endo*-cyclization of vinylepoxide

Completion of the total synthesis
1. Wittig coupling
2. H-ring: *S,O*-acetalization, radical reduction
3. Side chain: methylenation

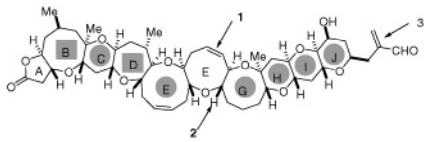


*Nakata's strategy for BTX-B (**1**)*

Synthesis of the ABCDEFG-ring
1. D-ring: SmI_2-induced cyclization
2. C- and E-rings: double SmI_2-induced cyclization
3. F-ring: 6-*endo*-cyclization of vinylepoxide
4. B-ring: 6-*endo*-cyclization of isopropenylepoxide
5. A-ring: RCM
6. G-ring: 6-*endo*-cyclization of methylepoxide

Synthesis of the IJK-ring
1. I-ring: SmI_2-induced cyclization
2. J-ring: 6-*endo*-cyclization of vinylepoxide
3. K-ring: SmI_2-induced Reformatsky reaction
4. Side chain: LA-mediated methallylation

Completion of the total synthesis
1. Wittig coupling
2. H-ring: *S,O*-acetalization, radical reduction

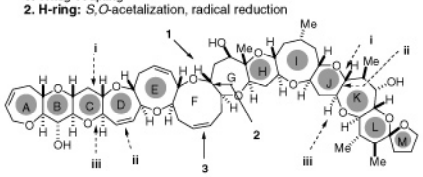


*Nicolaou's stratefgy for BTX-A (**2**)*

Synthesis of the BCDE-ring
1. C-ring: intramolecular Michael addition
2. B- and D-rings: double lactonization-alkylation-hydroboration
3. E-ring: vinylidation, single oxygen oxidation

Synthesis of the GHIJ-ring
1. J-ring: LA-mediated allylation
2. I-ring: 6-*endo*-cyclization of vinylepoxide
3. H-ring: 6-*endo*-cyclization of vinylepoxide
4. G-ring: *S,O*-acetalization, methylation

Completion of the total synthesis
1. Wittig coupling
2. E-ring: *S,O*-acetalization, radical reduction
3. A-ring: lactonization
4. Side chain: methylenation



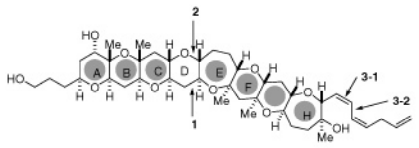
*Hirama's strategy for CTX3C (**5**)*

Syntheis of the ABCDE-ring
1. E-ring: aldol reaction of alkoxyacetate, RCM
1'. B-ring: LA-mediated allylation
2'. A-ring: RCM
2. D-ring: aldol reaction of alkoxyacetate, RCM
3. C-ring: acetalization, LA-mediated reduction

Synthesis of the HIJKLMN-ring
1. I-ring: aldol reaction of glycolate, RCM
2. H-ring: oxiranyl anion addition, 6-*endo*-cyclization
1'. L-ring: iodo-lactonization
2'. M-ring: Grignard addition, spiroacetalization
3. J-ring: intramolecular carbonyl olefination, hydroboration
4. K-ring: *O,O*-acetalization, LA-mediated Et_3SiH reduction

Completion of the total synthesis
1. acetal coupling, *S,O*-acetalization
2. G-ring: radical cyclization
3. F-ring: RCM

Second generation total synthesis
1. *S,O*-acetalization coupling
2. G-ring: radical cyclization
3. F-ring: RCM

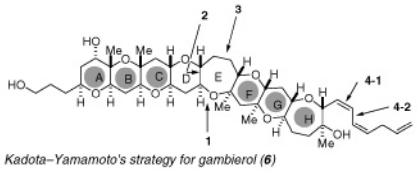


*Sasaki's strategy for gambierol (**6**)*

Synthesis of the ABC-ring
1. B-ring: 6-*endo*-cyclization of vinylepoxide
2. A-ring: intramolecular Michael addition
3. C-ring: 6-*endo*-cyclization of vinylepoxide

Synthesis of the EFGH-ring
1. H-ring: SmI_2-induced cyclization
2. G-ring: 6-*endo*-cyclization of vinylepoxide
3. F-ring: SmI_2-induced cyclization
4. E-ring: lactone enol phosphate, coupling, hydroboration

Completion of the total synthesis
1. *B*-alkyl Suzuki-Miyaura coupling
2. D-ring: *S,O*-acetalization, radical reduction
3. Side chain: coupling, coupling

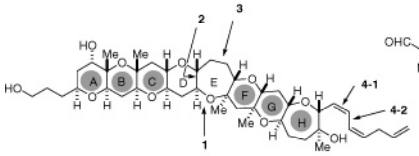


*Kadota–Yamamoto's strategy for gambierol (**6**)*

Synthesis of the ABC-ring
1. B-ring: 6-*endo*-cyclization of vinylepoxide
2. A-ring: intramolecular Michael addition
3. C-ring: SmI_2-induced cyclization

Synthesis of the FGH-ring
1. G-ring: 6-*endo*-cyclization of methylepoxide
2. F-ring: SmI_2-induced cyclization
3. H-ring: cyclization of γ-alkoxyallylstannane

Completion of the total synthesis
1. ester coupling
2. D-ring: cyclization of γ-alkoxyallylstannane
3. E-ring: RCM
4. Side chain: coupling, coupling

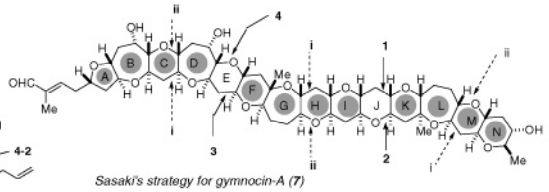


*Rainier's strategy for gambierol (**3**)*

Synthesis of the ABC-ring
1. A-ring: Diels-Alder addition, DMDO oxidn–allylation
2. B-ring: RCM, *m*CPBA oxidn, rearrangement
3. C-ring: RCM, DMDO oxidn–DIBAH reduction

Synthesis of the FGH-ring
1. G-ring: DMDO oxidn–allylation
2. F-ring: RCM, DMDO oxidn–DIBAH reduction
3. H-ring: acetalization, cyclic enol phosphate

Completion of the total synthesis
1. ester coupling
2. D-ring: RCM
3. E-ring: *S,O*-acetalization, radical reduction
4. Side chain: coupling, coupling



*Sasaki's strategy for gymnocin-A (**7**)*

Synthesis of the ABCD-ring
1. B-ring: lactone enol phosphate, Pd-catalyzed CO insertion, hydroboration
1'. D-ring: lactone enol phosphate, *B*-alkyl Suzuki–Miyaura coupling, hydroboration
2. C-ring: *S,O*-acetalization, radical reduction
3. A-ring: radical cyclization of idodo β-alkoxyacrylate

Synthesis of the KLMN(=FGHI)-ring
1. N (I)-ring: 6-*endo*-cyclization, *exo*-enol ether formation
1'. L (G)-ring: lactone enol phosphate, *B*-alkyl Suzuki–Miyaura coupling, hydroboration
2. M (H)-ring: acetalization, LA-mediated Et_3SiH reduction
3. K (F)-ring: lactone enol phosphate, (coupling, hydroboration)

Completion of the total synthesis
1. *B*-alkyl Suzuki-Miyaura coupling, hydroboration
2. J-ring: *S,O*-acetalization, radical reduction
3. *B*-alkyl Suzuki-Miyaura coupling, hydroboration
4. E-ring: *S,O*-acetalization, radical reduction

Figure 3. Synthetic strategies for large marine polycyclic ethers.

prominent member of marine polycyclic ethers. The structure was determined by spectroscopic and X-ray crystallographic analysis in 1989 by the groups of Lin, Nakanishi, and Clardy.[1] The structure consists

of a trans-fused six-,six-,six-,seven-,seven-,six-,six-, eight-,six-,six-,six-membered undecacyclic ether core (ABCDEFGHIJK-ring) containing 23 chiral centers and a side chain including an α-vinyl aldehyde moiety. BTX-B (**1**) exhibits potent neurotoxicity (LC_{50} = 16 ng) by binding to sodium channels, keeping them open and causing continual sodium ion influx.

The first and landmark total synthesis of BTX-B (**1**) was achieved by the Nicolaou group in 1995,[6] after a 12-year odyssey.[53] During these years toward BTX-B (**1**), they have made major contributions toward the improvement of the synthetic studies on marine polycyclic ethers: a number of new and effective synthetic methods and unique strategies have been developed. These methods have frequently and successfully been applied to the synthetic studies of marine polycyclic ethers by the Nicolaou group and also other groups as shown in this article. Recently, the second total synthesis of BTX-B (**1**) was stereoselectively and efficiently accomplished by the Nakata group.[12]

3.1. Nicolaou's Total Synthesis

The total synthesis of BTX-B (**1**) by Nicolaou et al. features the convergent strategy by coupling between the ABCDEFG- and IJK-rings, and final construction of the H-ring (Figure 3). The two segments and H-ring system were efficiently synthesized on the basis of their developed methods for the construction of cyclic ethers, that is, 6-*endo*-cyclization of hydroxy vinylepoxide, formation of cyclic enol ether followed by hydroboration, intramolecular Michael addition, and formation of cyclic *S*,*O*-acetal followed by radical reduction.

3.1.1. Synthesis of the ABCDEFG-ring

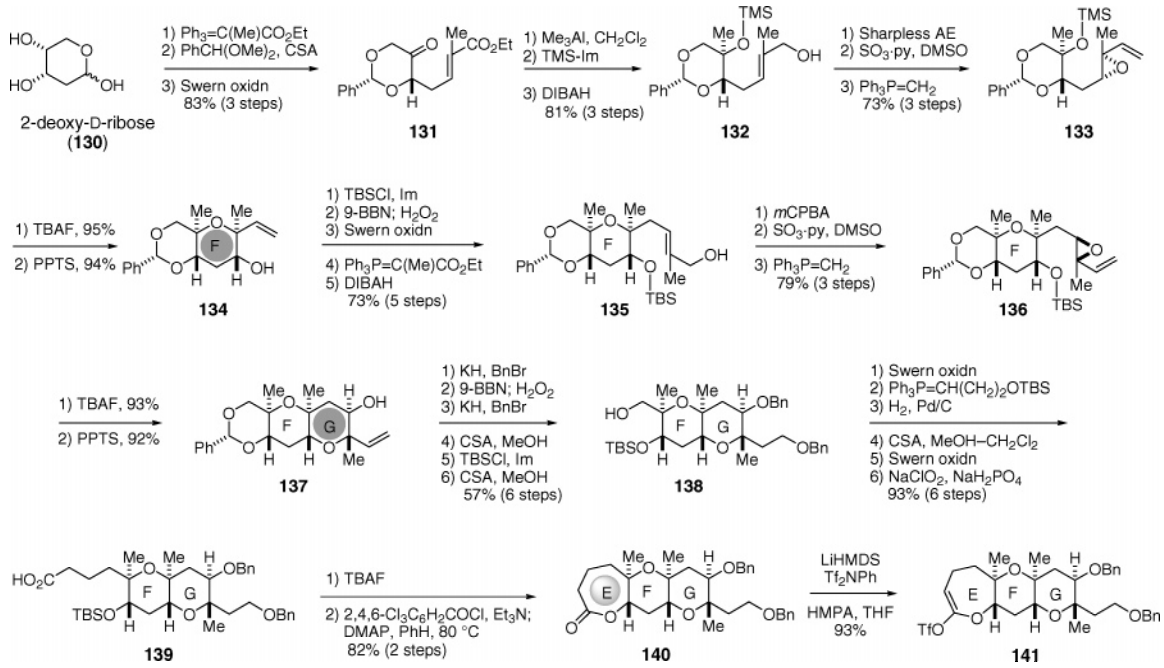
The synthesis of the ABCDEFG-ring **158** started with 2-deoxy-D-ribose (**130**) (Schemes 8 and 9). The construction of the F- and G-rings was effectively achieved by 6-*endo* cyclization of hydroxy vinylepoxide[23] (Scheme 8). Treatment of ketone **131** with Me_3Al exclusively afforded the α-methyl adduct, which was silylated and reduced with DIBAH to give allyl alcohol **132**. The Sharpless AE of **132** stereoselectively afforded α-epoxide, which was subjected to oxidation with SO_3·py−DMSO and Wittig olefination to give vinylepoxide **133**. After removal of the TMS group, treatment of **133** with PPTS stereoselectively induced 6-*endo*-cyclization to give the F-ring **134** (94%), which was converted to allyl alcohol **135** in straightforward steps. Epoxidation of **135** with *m*CPBA exclusively afforded β-epoxide, which was again subjected to SO_3·py oxidation and Wittig olefination to give vinylepoxide **136**. After removal of the TBS group, treatment of **136** with PPTS again effected stereoselective 6-*endo*-cyclization to give the FG-ring **137** (92%). Conversion of **137** to alcohol **138**[54] followed by chain elongation led to carboxylic acid **139**, which after desilylation was treated under Yamaguchi's conditions[27] to give seven-memberd lactone **140**. To construct the functionalized E-ring, a side chain was introduced via Murai coupling[29] of cyclic enol triflate and a higher order organocuprate. The required cyclic enol triflate **141** was prepared from the lactone **140** by treatment with LiHMDS and $PhNTf_2$.

The construction of the ABCDEFG-ring system was further carried out (Scheme 9). Treatment of iodide **142** with *t*-BuLi and then (2-thienyl)(CN)CuLi followed by addition of **141** afforded a 2.4:1 mixture of the desired α-methyl-**143a** and its β-methyl epimer **143b**, after hydrolysis. Hydroboration of the mixture **143** followed by hydrolysis stereoselectively afforded the functionalized E-ring carboxylic acid **144**. The Yamaguchi lactonization of **144** afforded the desired α-methyl lactone **145a** (60%) and its β-methyl epimer **145b** (25%), which were separated by silica gel chromatography. The undesired **145b** could be converted to a 1:1 mixture of **145a** and **145b** in six steps.[55] The desired α-methyl lactone **145a** was again treated with LiHMDS and $PhNTf_2$ to give cyclic enol triflate **146**. Cr(II)−Ni(II)-mediated coupling[56] of triflate **146** and aldehyde **147** under sonication conditions effectively provided cyclic enol ether **148**. Removal of the hydroxyl group in **148** followed by hydroboration stereoselectively afforded the D-ring **149**. Side chain elongation of **149** via HWE reaction led to α,β-unsaturated ester **150**, which upon treatment with KH in THF underwent an intramolecular hetero-Michael addition to give the C-ring **151** (90%) as a single product. The ester **151** was stereoselectively converted to vinylepoxide **153** through Sharpless AE of **152**. Treatment of **153** with PPTS stereoselectively induced 6-*endo*-cyclization to give the B-ring **154** (76%), after silylation, which was converted to methyl ketone **155** in a standard manner. The HWE ester **156**, prepared from **155**, was treated with *i*-Pr_2NEt and LiCl to afford α,β-unsaturated-δ-lactone **157**. Here, the A-ring lactone **157** was masked as the A-ring cyclic ether by DIBAH reduction followed by BF_3·Et_2O-mediated Et_3SiH reduction. Subsequent functional group manipulation led to phosphonium salt **158**, corresponding to the ABCDEFG-ring.

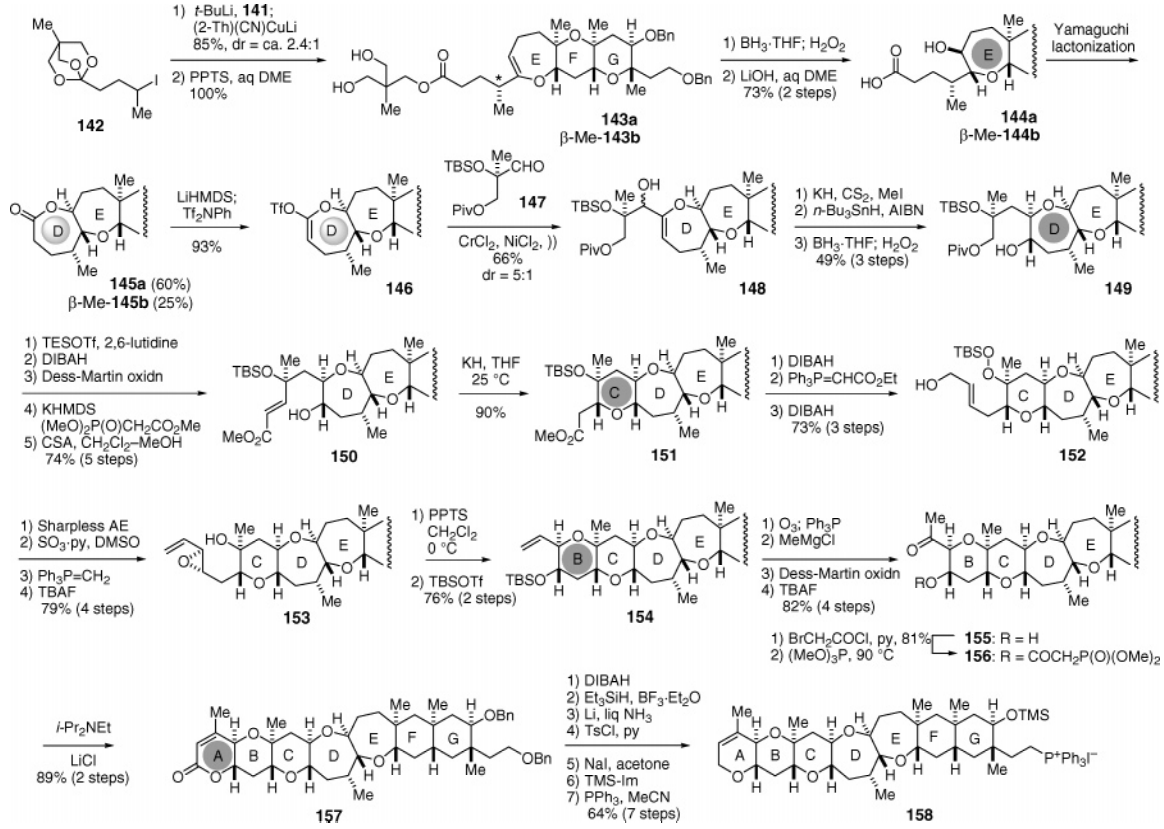
3.1.2. Synthesis of the IJK-ring

The synthesis of the IJK-ring **169** started with the key intermediate **12**[5] for their total synthesis of HBTX-B (**3**) (Scheme 10). Deprotection of the acetonide **12**, selective benzylation, and Swern oxidation afforded ketone, which was treated with Me_3Al in the presence of $MgBr_2$·Et_2O to give a 3:1 mixture of α-methyl adduct **159** (61%) and the β-methyl isomer (20%). Ozonolysis of the olefin **159** followed by Grignard reaction afforded α-alcohol **160** and its β-isomer in a ratio of 1:1. After conversion of **160** to α,β-unsaturated ester **161**, the J-ring was constructed by intramolecular hetero-Michael addition; treatment of **161** with NaH in THF induced stereoselective cyclization to give the JK-ring **162** (70%), which was converted to allyl alcohol **163** in three steps. Treatment of **163** with *m*CPBA effected stereoselective epoxidation to give β-epoxide (dr = 10:1), which was converted to α,β-unsaturated ester **164**. CSA treatment of **164** in CH_2Cl_2 stereoselectively effected 6-*endo*-cyclization to give the I-ring **165** (70%). Functional group manipulation including side chain elon-

Scheme 8



Scheme 9

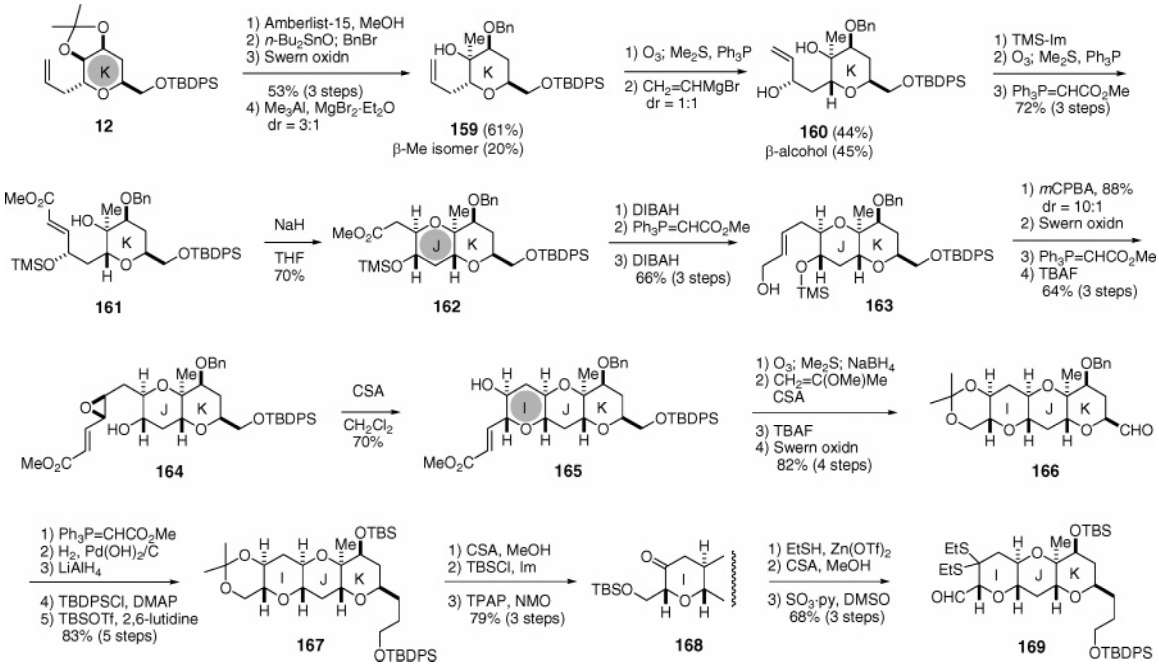


gation led to ketone **168**, which was converted to aldehyde **169**, corresponding to the IJK-ring, via thioacetalization, desilylation, and SO_3·py oxidation.

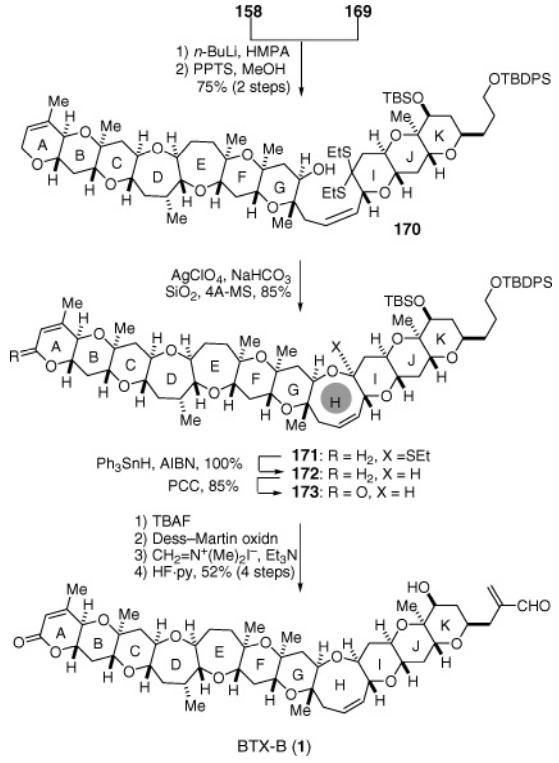
3.1.3. Completion of the Total Synthesis

The Wittig coupling of the phosphonium salt **158** and the aldehyde **169** afforded (*Z*)-olefin **170** (75%) after removal of the TMS group (Scheme 11). Treatment of **170** with $AgClO_4$ effected cyclization of hydroxy dithioacetal to give eight-membered *S*,*O*-acetal **171** (85%), which was reduced by Ph_3SnH-AIBN to give the H-ring **172** quantitatively. Treatment of **172** with PCC effected oxidation of the A-ring methylene to give δ-lactone **173**. Removal of the TBDPS group followed by Dess−Martin oxidation afforded aldehyde, which was treated with Eschenmoser's salt to give α-vinyl aldehyde. Final desilylation with HF·py furnished BTX-B (**1**).

Scheme 10



Scheme 11



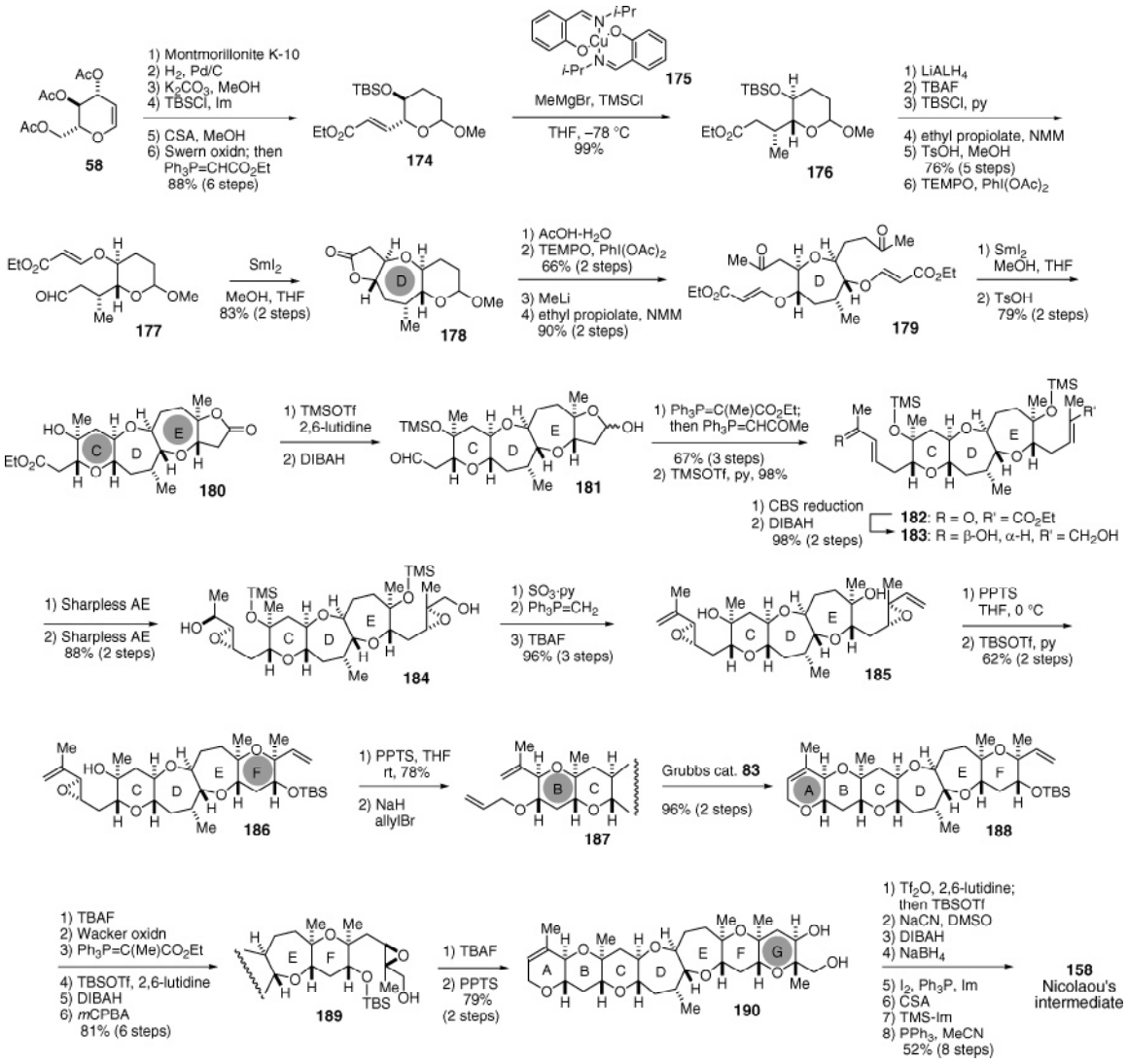
3.2. Nakata's Total Synthesis

The Nakata group recently achieved the second and stereoselective total synthesis of BTX-B (**1**),[12] in which their developed SmI_2-induced cyclization[57] was often used for the construction of cyclic ether rings, and several kinds of double reactions were efficiently used for the synthesis of the left segment (Figure 3). A similar convergent strategy as Nicolaou's synthetic route was carried out for coupling of the two segments, ABCDEFG- and IJK-rings.

3.2.1. Synthesis of the ABCDEFG-ring

The synthesis of the left segment **158**, corresponding to the ABCDEFG-ring, started with tri-*O*-acetyl-D-glucal (**58**) (Scheme 12). The first task was a stereoselective introduction of the α-methyl group to α,β-unsaturated ester **174**, prepared from **58**. After several experiments, it was found that Kuwajima's conditions[58] smoothly effected the Michael addition; upon treatment of **174** with MeMgBr and TMSCl in the presence of Cu(N-*i*-Pr−Sal)$_2$ catalyst **175**, the addition efficiently and stereoselectively took place to give only α-methyl adduct **176** in 99% yield. The ester **176** was converted to aldehyde **177** via hetero-Michael addition with ethyl propiolate in the presence of *N*-methyl morpholine (NMM). Treatment of **177** with SmI_2 in the presence of MeOH in THF induced reductive cyclization with concomitant lactonization to give seven-membered D-ring **178** with complete stereoselection. After hydrolysis of the acetal **178** followed by TEMPO oxidation, treatment of the resulting bis(lactone) with MeLi and with ethyl propiolate efficiently underwent double methylation and double hetero-Michael addition, respectively, to give bis(β-alkoxyacrylate) **179**. Reaction of **179** with SmI_2 induced the desired double cyclization with complete stereoselection to give trans-fused ester-lactone **180** (79%), corresponding to the CDE-ring, after complete lactonization by TsOH treatment. TMS protection of **180** followed by DIBAH reduction afforded aldehyde-lactol **181**. One-pot Wittig reaction using $Ph_3P{=}C(Me)CO_2Et$ at room temperature and then $Ph_3P{=}CHCOMe$ at 90 °C efficiently afforded ketone-ester **182**, after TMS protection. The CBS asymmetric reduction[59] of the ketone **182** followed by DIBAH reduction gave allyl alcohol **183**. Consecutive Sharpless AE of **183** with TBHP/(−)-DIPT and then TBHP/(+)-DIPT effected regio- and stereoselective epoxidation at the right and left sides, respectively, to afford bis(α-epoxide) **184**. Double oxidation of the

Scheme 12



diol **184** with SO_3·py-DMSO, double Wittig reaction with $Ph_3P{=}CH_2$, and removal of two TMS groups afforded bis(vinylepoxide) **185**. Treatment of **185** with PPTS at 0 °C effected 6-*endo*-cyclization at the right side to give **186** after TBS protection. Subsequent treatment of **186** with PPTS at room temperature induced 6-*endo*-cyclization at the left side to give the B-ring, which was allylated to give ally ether **187**. RCM of **187** with Grubbs catalyst **83** smoothly provided the A-ring ether **188**, which was converted to the desired β-epoxide **189** via stereoselective epoxidation with *m*CPBA. After removal of the TBS group, treatment of the methylepoxide **189** with PPTS effected 6-*endo*-cyclization without any activation[60] to give the G-ring **190**, which was successfully converted to the Nicolaou's key intermediate, phosphonium salt **158**,[6] corresponding to the ABCDEFG-ring, in straightforward steps.

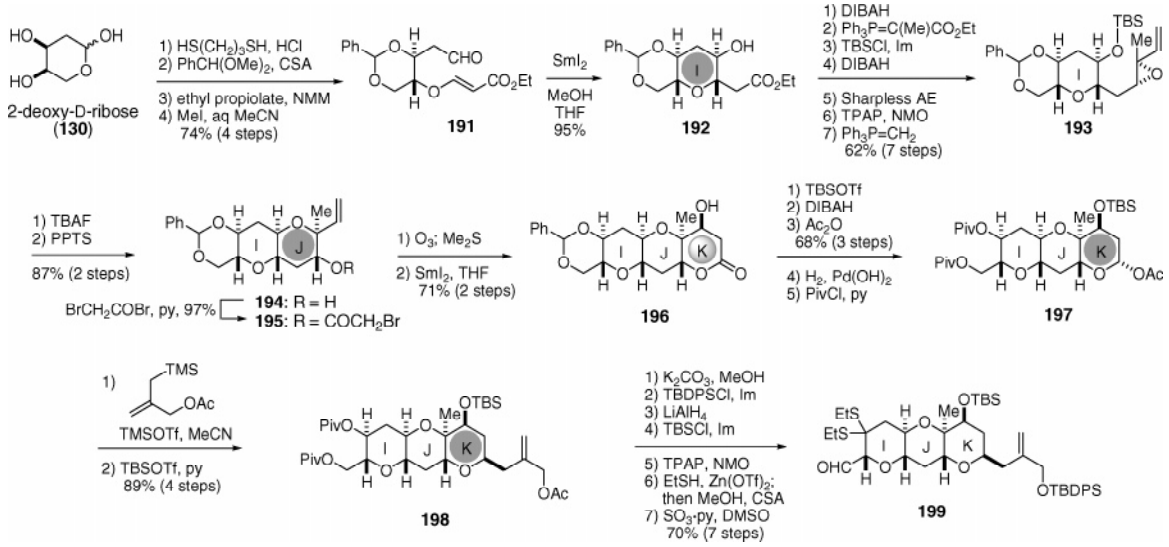
3.2.2. Synthesis of the IJK-ring

The synthesis of the IJK-ring system **199** started with 2-deoxy-D-ribose (**130**) (Scheme 13). SmI_2-induced cyclization of aldehyde **191** stereoselectively gave the desired I-ring **192** in 95% yield. The ester **192** was stereoselectively converted to vinylepoxide **193** in straightforward steps including Wittig reaction and Sharpless AE. After removal of the TBS group, treatment of **193** with PPTS effected 6-*endo*-cyclization to give the IJ-ring **194** (87%), which was acylated to bromoacetate **195**. Subsequent oxidative cleavage of the olefin in **195** and SmI_2-promoted Reformatsky-type reaction[61] of the resulting aldehyde stereoselectively afforded δ-lactone **196** (71%) having the desired β-axial alcohol. Functional and protective group manipulations led to acetate **197**. The carbon four unit as the side chain was directly introduced under the same procedure in their total synthesis of HBTX-B (**3**); treatment of **197** with $CH_2{=}C(CH_2OAc)$-CH_2TMS in the presence of TMSOTf afforded **198**, after TBS protection. The dipivalate **198** was converted to the fully functionalized right segment **199**, corresponding to the IJK-ring, in straightforward steps.

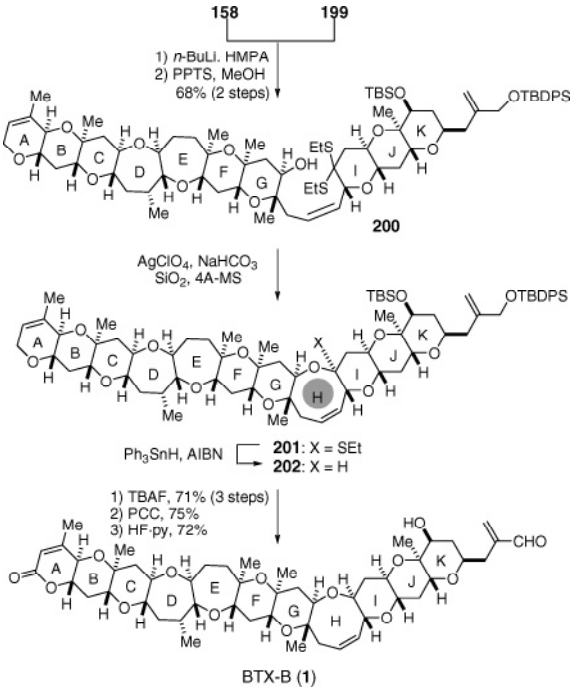
3.2.3. Completion of the Total Synthesis

The coupling of the left and right segments, **158** and **199**, and construction of the H-ring were realized following Nicolaou's conditions[6] (Scheme 14). Treatment of **158** with *n*-BuLi followed by addition of **199** induced their coupling to give (*Z*)-olefin **200**, after

Scheme 13



Scheme 14



removal of the TMS group. Treatment of **200** with $AgClO_4$ afforded eight-membered *S*,*O*-acetal **201**, which was reduced with Ph_3SnH in the presence of AIBN to give the H-ring **202**. After removal of the TBDPS group, both sides were doubly oxidized by PCC treatment to give lactone−aldehyde. Final deprotection of the TBS group with HF·py furnished BTX B (**1**).

4. Total Synthesis of Brevetoxin-A

In 1986, the structure of BTX-A (**2**) was determined by Shimizu et al. by spectroscopic and X-ray crystallographic analyses.[62] The structure consists of a trans-fused five-,eight-,six-,seven-,nine-,eight-,eight-, six-,six-,six-membered decacyclic ether core (ABC-DEFGHIJ-ring) containing 22 chiral centers, γ-lactone, and a side chain including an α-vinyl aldehyde moiety.

The first and only total synthesis of BTX-A (**2**) in 1998 was achieved by Nicolaou's group via the coupling of the BCDE- and GHIJ-rings (Figure 3).[7]

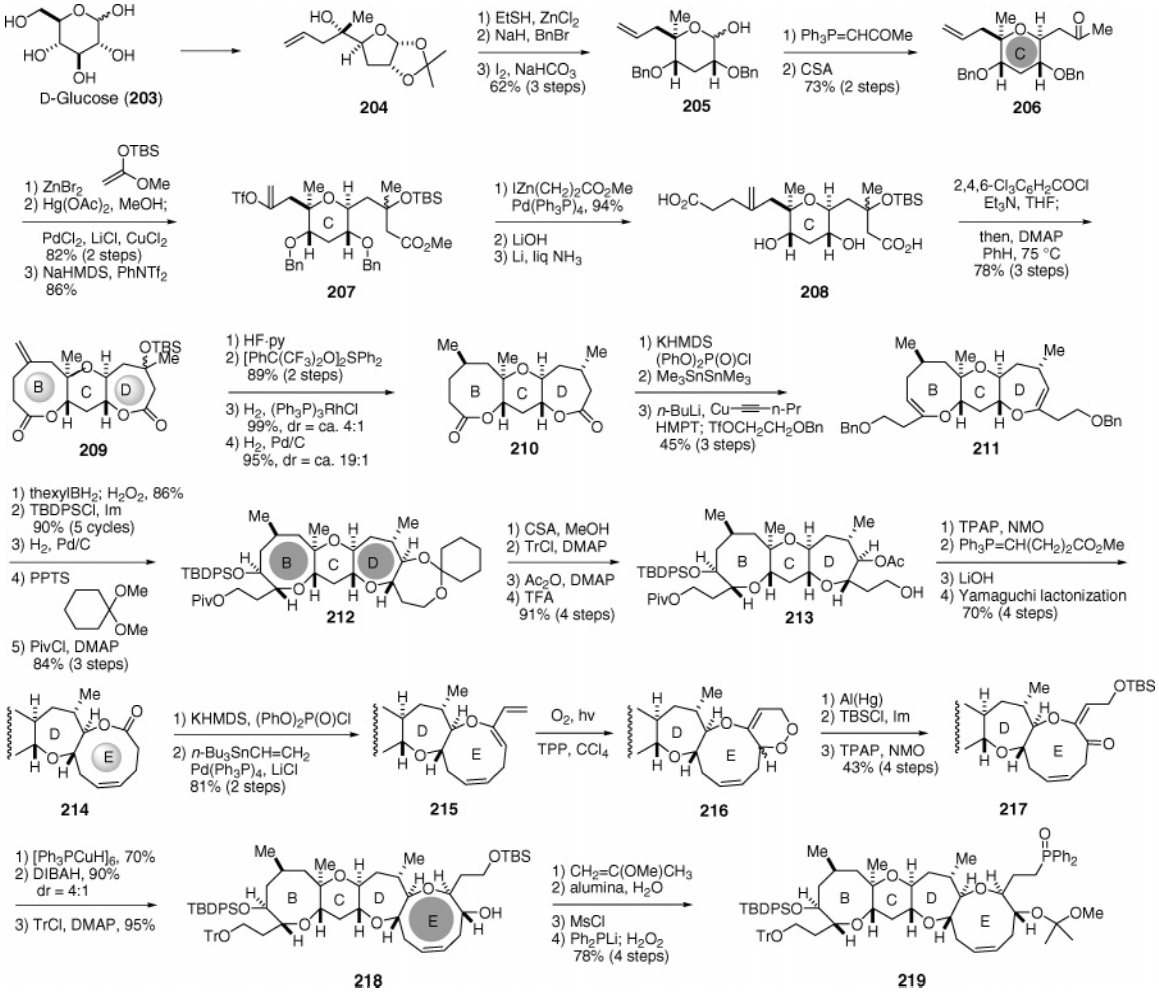
4.1. Nicolaou's Total Synthesis

4.1.1. Synthesis of the BCDE-ring

The synthesis of the BCDE-ring **219** was accomplished starting from D-glucose (**203**) via bis(lactone) **210** (Scheme 15). The C-ring was constructed by an intramolecular hetero-Michael addition, and the B- and D-rings were synthesized through two-directional strategy via each double reaction concerning lactonization, formation of cyclic enol ether, and hydroboration. The E-ring was constructed via diene **215** derived from nine-membered lactone **214**.

The Wittig reaction of **205**, prepared from **203** via **204**, with Ph_3P=CHCOMe followed by CSA treatment induced an intramolecular hetero-Michael addition to provide tetrahydropyran **206** (73%), corresponding to the C-ring. Addition of CH_2=C(OMe)-OTBS to the ketone **206** and subsequent oxymercuration−palladation provided methyl ketone, which was converted to vinyl triflate **207** by treatment with NaHMDS−$PhNTf_2$. After coupling with $IZn(CH_2)_2$-CO_2Me in the presence of $Pd(Ph_3P)_4$, hydrolysis followed by debenzylation led to dicarboxylic acid **208**, which was subjected to Yamaguchi's lactonization to give bis(lactone) **209**. Desilylation followed by dehydration by Martin's sulfurane[63] afforded doubly unsaturated bis(lactone), whose D- and B-rings were sequentially hydrogenated with Wilkinson catalyst (dr = ca. 4:1) and then with Pd/C (dr = ca. 19:1), respectively, to give bis(lactone) **210** having two methyl groups with the desired stereochemistry. Conversion of **210** to tricyclic enol ether **211** was realized by an efficient two-directional approach. Treatment of the bis(lactone) **210** with KHMDS and $(PhO)_2P(O)Cl$ followed by $Me_3SnSnMe_3$−$Pd(Ph_3P)_4$−LiCl afforded bis(vinylstannnane), which was treated with *n*-BuLi, CuC≡C-*n*-Pr, and HMPT, and then $BnOCH_2CH_2OTf$ to give bis(cylic enol ether) **211**. After stereoselective hydroboration with thexylbo-

Scheme 15

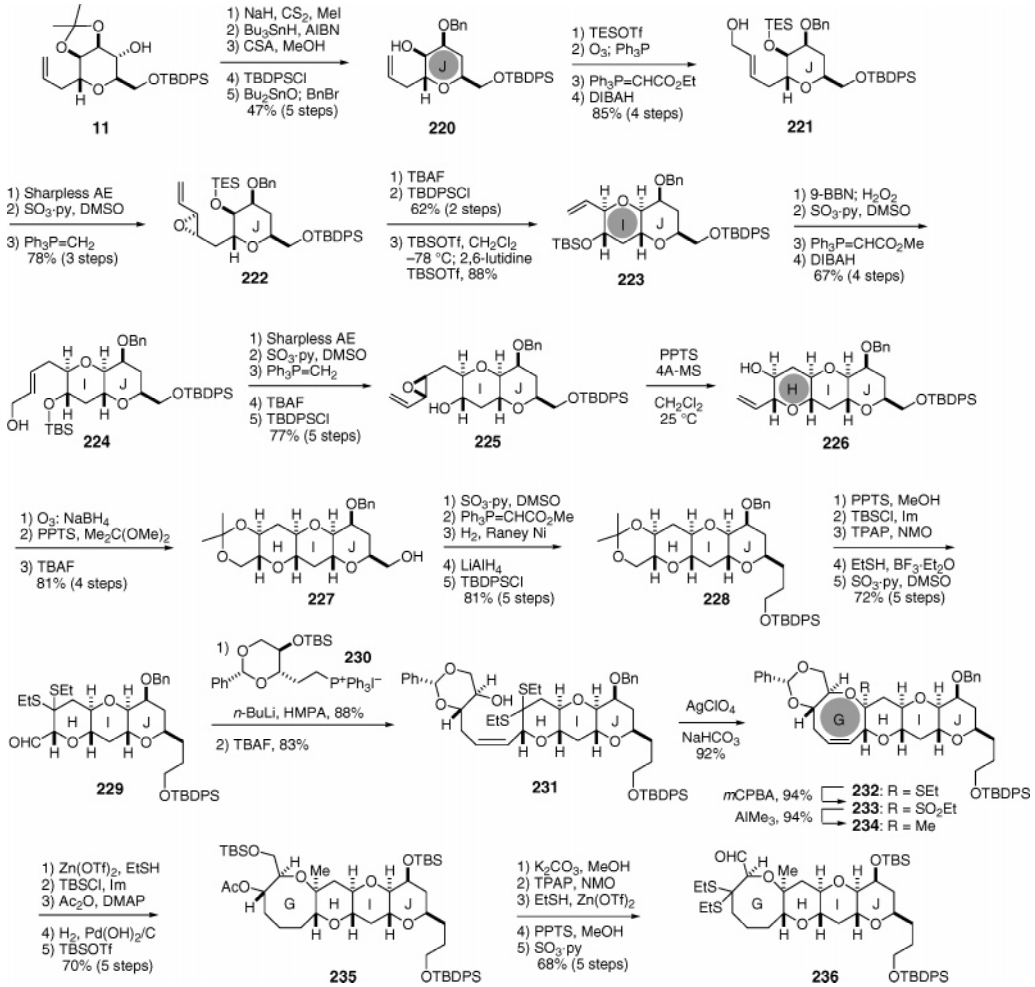


rane at both sides followed by selective monosilylation, subsequent hydrogenolysis of two benzyl groups, and acetal and pivaloyl protections afforded **212**, successfully differentiating the left and right sides. After protective group manipulation, the resulting alcohol **213** was converted to nine-membered lactone **214** via Wittig olefination and Yamaguchi lactonization. Conversion of **214** to the enol phosphate followed by palladium-catalyzed coupling with n-$Bu_3SnCH{=}CH_2$ afforded conjugated diene **215**. Treatment with singlet O_2 induced selective [4 + 2] cycloaddition to give endoperoxide **216**, which was subjected to reductive cleavage with Al(Hg), selective TBS protection, and TPAP oxidation to give enone **217**. Sequential reduction with $[(Ph_3P)CuH]_6$ and with DIBAH provided diol (dr = 4:1), which was selectively protected to give trityl ether **218**. Protection of the alcohol **218** as a mixed methoxyacetal, selective removal of the TBS group, mesylation, and displacement with $LiPPh_2$ followed by oxidation with H_2O_2 furnished the desired phosphine oxide **219**, corresponding to the BCDE-ring system.

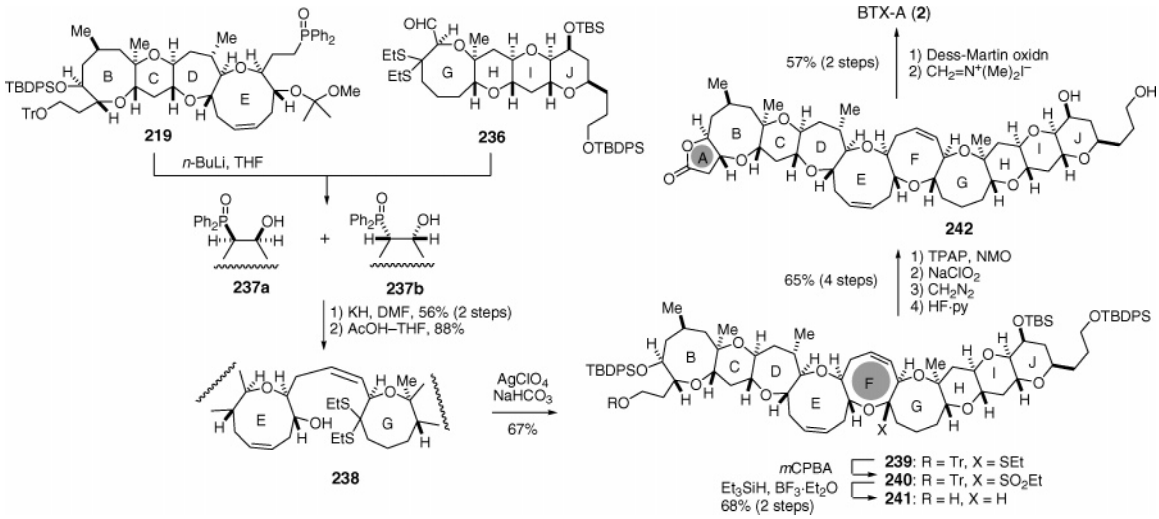
4.1.2. Synthesis of the GHIJ-ring

The synthesis of the GHIJ-ring started with the alcohol **11**,[5] the key intermediate in their total synthesis of HBTX-B (**3**) (Scheme 16). The alcohol **11** was converted to allyl alcohol **221** via **220** in a standard procedure. The Sharpless AE of **221**, SO_3·py oxidation, and Wittig olefination stereoselectively gave vinylepoxide **222**. After removal of the TES group, the desired 6-*endo*-cyclization and silylation were performed in a one-pot procedure by successive addition of TBSOTf (0.24 equiv) and then TBSOTf (1.05 equiv)−2,6-lutidine to give **223** in 88% yield. After the functional group manipulation, the resulting allyl alcohol **224** was again converted to hydroxy vinylepoxide **225** via Sharpless AE and Wittig olefination. Treatment of **225** with PPTS effected stereoselective 6-*endo*-cyclization to give tetrahydropyran **226**, corresponding to the HIJ-ring. Functional group manipulation including chain elongation led to aldehyde **229** through **227** and **228**. The Wittig coupling of **229** with the ylide derived from **230** efficiently afforded (*Z*)-olefin **231**, after desilylation. The hydroxy dithioketal **231** was cyclized to the eight-membered *S*,*O*-acetal **232** by treatment with $AgClO_4$. After *m*CPBA oxidation of **232** to **233**, an angular methyl group was efficiently and stereoselectively introduced by treatment with $AlMe_3$[52] to give **234**. After protective group manipulation, hydrogenation of the double bond in **234** was carried out with concomitant debenzylation to give **235**, after TBS protection. The TBS ether **235** was converted to aldehyde **236**, corresponding to the GHIJ-ring, in a standard manner.

Scheme 16



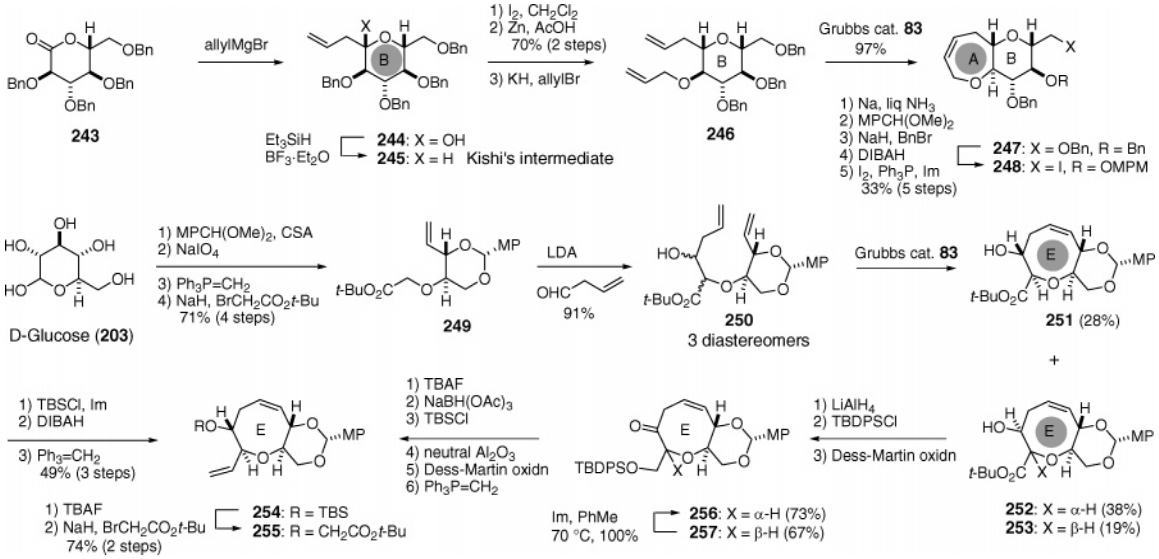
Scheme 17



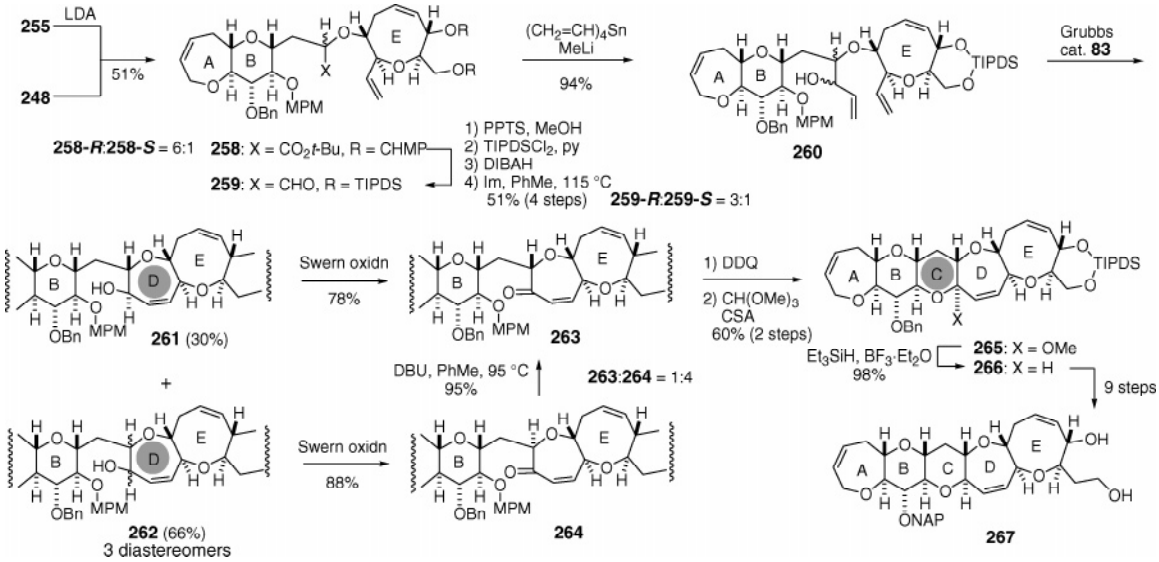
4.1.3. Completion of the Total Synthesis

The total synthesis of BTX-A (**2**) was completed through the coupling of the BCDE- and GHIJ-rings, **219** and **236** (Scheme 17). Treatment of **219** with *n*-BuLi followed by addition of **236** afforded two diastereomeric hydroxy phosphine oxides **237a** and **237b**, which were converted by KH treatment to a single (*Z*)-olefin **238**, after hydrolysis of the methoxy acetal. Subsequent $AgClO_4$-induced cyclization of **238** to *S*,*O*-acetal **239** followed by *m*CPBA oxidation provided sulfone **240**, which was subjected to LA-mediated Et_3SiH reduction to give eight-membered F-ring **241**. The A-ring γ-lactone **242** was constructed via oxidation to a carboxylic acid, esterification, and HF·py treatment, which induced simultaneous desilylation and lactonization. Finally, Dess–Martin oxidation of the primary alcohol in **242** followed by

Scheme 18



Scheme 19



treatment with Eschenmoser's salt furnished BTX-A (**2**).

5. Total Synthesis of Ciguatoxin CTX3C

In 1989, Yasumoto et al. determined the structure of ciguatoxin (CTX, **4**), produced by the marine dinoflagellate *Gambierdiscus toxicus*.[64] To date, the structures of more than 20 congeners including CTX3C[65] (**5**) were also determined.[66] Causative toxins accumulate in fish of many species through the food chain and exert strong toxicity through the activation of voltage-sensitive sodium channels. The complex structure consists of seven-,six-,six-,seven-,eight-, nine-,seven-,six-,eight-,six-,seven-,six-,five-membered tridecacyclic ether core (ABCDEFGHIJKLM-ring) containing 30 chiral centers, 5,6-spiroacetal, and four double bonds, three hydroxyl groups and five methyl groups on the ether rings.

The first total synthesis of CTX3C (**5**) by the Hirama group in 2001 has been achieved on the basis of a highly convergent strategy featuring the chemoselective RCM reaction as a key tactic (Figure 3).[8] They further improved the total synthsis and also reported second generation total synthesis of CTX3C (**5**).[67]

5.1. Hirama's Total Synthesis

5.1.1. Synthesis of the ABCDE-ring

The synthesis of the ABCDE-ring system **267** was accomplished via an alkylative coupling between the AB-ring iodide **248** and the E-ring alkoxyacetate **255**, and successive construction of the D- and C-rings by RCM reaction and by LA-mediated reductive etherification, respectively (Schemes 18 and 19).

The synthesis of the AB-ring started with Kishi's intermediate **245**,[68] which was prepared via Grignard allylation of **243** followed by LA-mediated Et_3SiH reduction of **244** (Scheme 18). Selective removal of the benzyl group using Nicotra's method[69] (I_2 cyclization; Zn reduction) followed by *O*-allylation afforded allyl ether **246**. RCM reaction of **246** using Grubbs catalyst **83** efficiently constructed the 7,6-bicyclic AB-ring **247** in 97% yield, which was converted to the desired AB-ring iodide **248** in five steps.

The synthesis of the E-ring started with D-glucose (**203**), which was converted to alkoxyacetate **249** via MP acetalization, oxidative cleavage of the diol, Wittig olefination, and coupling with $BrCH_2CO_2t$-Bu (Scheme 18). Subsequent aldol condensation of **249** with 3-butenal afforded an inseparable mixture of three diastereomers **250**. RCM reaction of the mixture **250** using Grubbs catalyst **83** provided eight-membered cyclic ethers **251**, **252**, and **253** in 28%, 38%, and 19% yields, respectively. The alcohol **251** with the correct configuration was readily converted to the E-ring **255** having an alkoxyacetate group via **254**. The diastereomers **252** and **253** were also converted into the desired **255** via epimerization of ketone **257** to **256** and stereoselective reduction with $NaBH(OAc)_3$.

The left ABCDE-ring system **267** was then constructed through alkylative coupling of the E-ring alkoxyacetate **255** and the AB-ring iodide **248** (Scheme 19). Coupling of the lithium enolate of **255** and the iodide **248** gave alkylated adduct **258** in 51% yield as an inseparable epimeric mixture in favor of the undesired stereoisomer (R/S = 6:1). To obtain the desired isomer, epimerization was examined as follows. After protective group manipulation, DIBAH reduction of the esters afforded aldehydes **259**. Epimerization of **259** (R/S = 6:1) with imidazole in toluene at 110 °C afforded an inseparable 3:1 mixture **259-*R*** and **259-*S***, which was treated with vinyllithium to give a mixture of four diastereomers **260**. RCM reaction of **260** with Grubbs catalyst **83** gave a mixture of four cyclized products, **261** (30%) and **262** (66%, three diastereomers). The Swern oxidation of the desired **261** with the correct configuration afforded ketone **263**. The other three diastereomers **262** were also converted into a 1:4 mixture of ketones **263** and **264** via Swern oxidation followed by epimerization with DBU. Removal of the MPM group followed by intramolecular acetalization afforded methyl acetal **265**, which was subjected to LA-mediated reductive etherification to give the ABCDE-ring segment **266** in 98% yield. Subsequent functional group manipulation furnished the NAP-protected ABCDE-ring system **267**.

5.1.2. Synthesis of the HIJKLM-ring

The synthesis of the HIJKLM-ring system **291** was accomplished via esterification between the HI-ring alcohol **276** and the LM-ring carboxylic acid **284**, and successive construction of the J- and K-rings by intramolecular carbonyl olefination and by LA-mediated reductive etherification, respectively (Schemes 20 and 21).

The synthesis of the HI-ring **276** started with 2-deoxy-D-ribose (**130**) (Scheme 20). The Wittig olefination of **130**, protection as the MP acetal, *O*-alkylation with *tert*-butyl bromoacetate, and aldol reaction with acrolein afforded the desired adduct 33*R*-**268** (44%) along with the 33*S*-epimer (44%). RCM reaction of 33*R*-**268** with Grubbs catalyst **83** provided the eight-membered I-ring **269** in 75% yield, which was converted to enone **270**. The Michael addition of **270** with $Me_2Cu(CN)Li_2$ gave α-methyl adduct as a single isomer, which was desilylated and stereoselectively reduced with $NaBH(OAc)_3$ to give diol **271**. The H-ring was constructed by applying Mori's oxiranyl anion strategy.[39] After one-pot treatment with Tf_2O and TESOTf, addition of the lithiated epoxysulfone **272** afforded adduct **273**, which upon treatment with TsOH was cyclized to six-membered ketone **274** (46% from **271**). $NaBH_4$ reduction of **274** stereoselectively afforded the desired β-alcohol, which was transformed to nitrile **275**. Subsequent DIBAH reduction of **275** followed by thioacetalization and removal of the TES group afforded the desired HI-ring thioacetal **276**.

The synthesis of the LM-ring started with benzyl-(*S*)-glycidol (**277**) (Scheme 20). The Ireland−Claisen rearrangement of **278**[70] followed by esterification afforded a 3:1 mixture of the desired **279** and its C48-epimer in 88% yield. Treatment of **279** with I_2 followed by hydrolysis provided δ-lactone **280**. After MOM protection, addition of allyl-MgBr followed by hydroboration and acid treatment afforded the 5,6-spiroacetal **281**, corresponding to the LM-ring. After debenzylation followed by Swern oxidation, the resulting aldehyde was subjected to Roush asymmetric allylation[71] using **282** to give **283** stereoselectively. Subsequent protection of the alcohol **283** as the NAP ether, oxidative cleavage of the olefin, and oxidation provided the LM-ring carboxylic acid **284**.

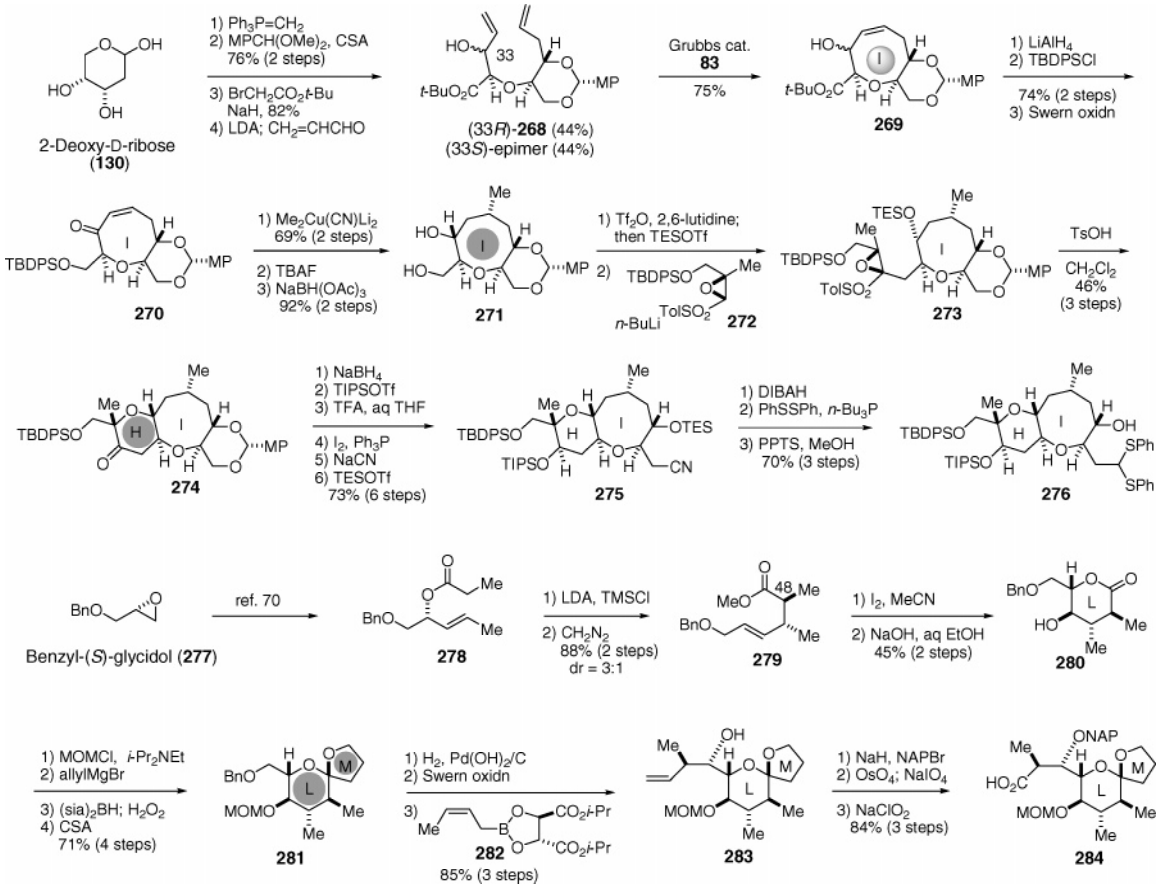
The coupling of the HI-ring alcohol **276** and the LM-ring carboxylic acid **284** under Yamaguchi's conditions[27] afforded ester **285**. RCM reaction toward cyclic enol ether **286** using Tebbe reagent,[72] Schrock catalyst **82**, or Grubbs catalysts **83** and **84** gave unsatisfactory results, presumably because of steric hindrance around the acyclic *exo*-enol ether. This problem was overcome by Takeda's protocol: carbonyl olefination reaction of titanium carbenes.[73] Reaction of **285** with the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ effectively afforded the desired cyclic enol ether **286** in 80% yield. Subsequent hydroboration followed by Dess−Martin oxidation afforded the desired J-ring **287** and its epimer **288** in a ratio of 1:3. Isomerization of **288** with DBU afforded a 1:2 mixture of **287** and **288**. The K-ring was constructed via cyclic *O*,*O*-acetal formation and LA-mediated Et_3-SiH reduction to give **289**. After selective removal of the TBDPS group followed by SO_3·py oxidation, the resulting aldehyde was treated with $allylSnBu_3$−$MgBr_2$·Et_2O to give the desired β-alcohol **290**. Finally, NAP protection followed by oxidative cleavage of the double bond provided the required HIJKLM-ring aldehyde **291**.

5.1.3. Completion of the Total Synthesis

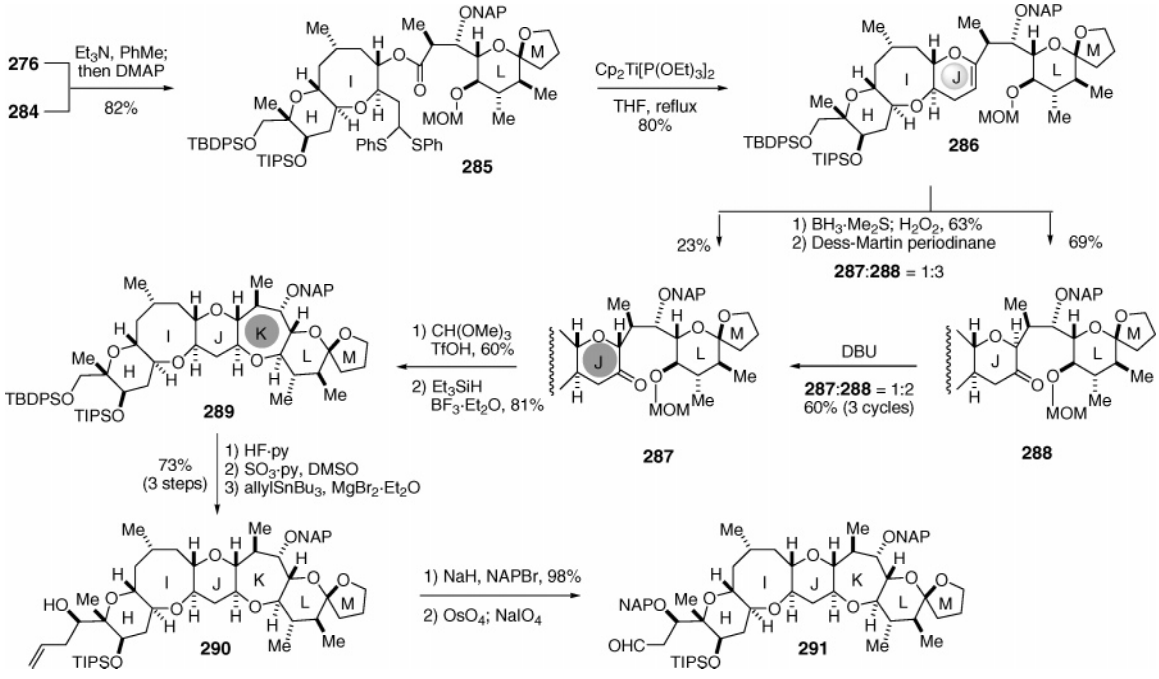
With the ABCDE-ring **267** and the HIJKLM-ring **291**, the stage was now set for the union of both segments toward the completion of the total synthesis of CTX3C (**5**) (Scheme 22). The total synthesis was accomplished via the union of both segments **267** and **291** by acetalization to the seven-membered *O*,*O*-acetal **292**, conversion to the linear *S*,*O*-acetal **293**, and construction of the G- and F-rings by radical cyclization and RCM, respectively.

$Sc(OTf)_3$-promoted condensation between the aldehyde **291** and the diol **267** afforded seven-mem-

Scheme 20

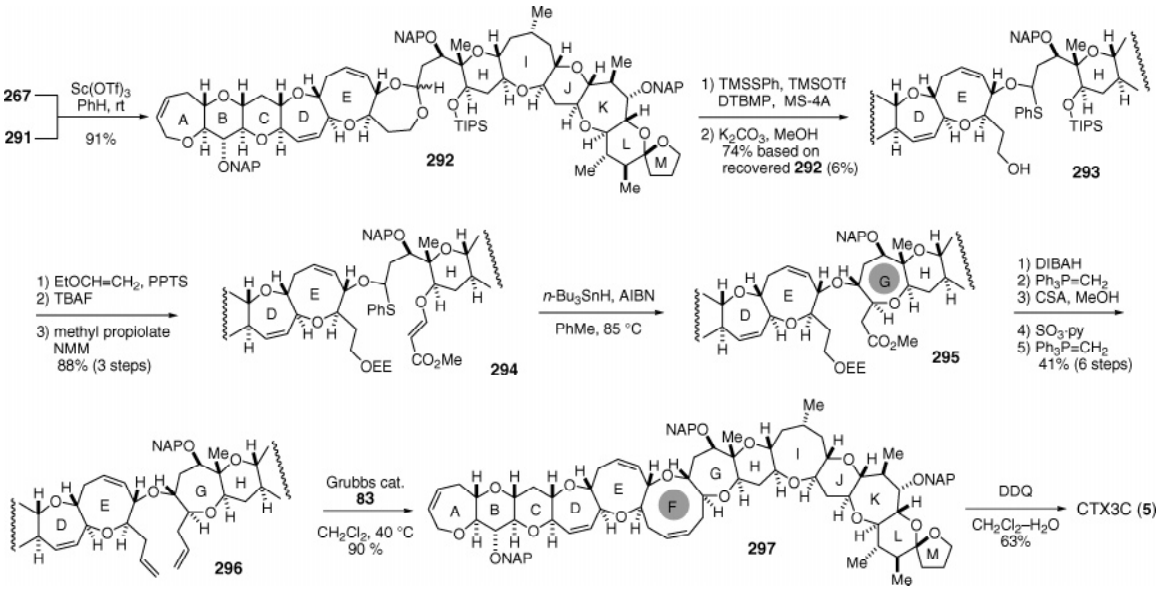


Scheme 21

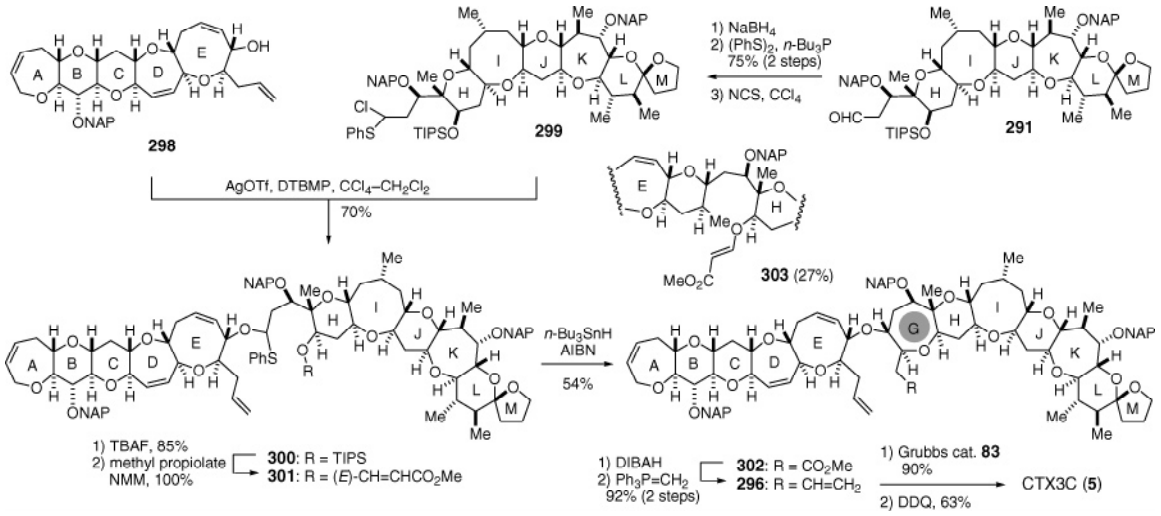


bered acetal **292** in 91% yield. Treatment of the acetal **292** with PhSTMS, TMSOTf, and DTBMP effectively afforded the desired linear *S*,*O*-acetal **293** in 74% yield based on the recovered **292** (6%), after removal the TMS group on the primary alcohol. The construction of the G-ring was performed by modification of the Sasaki procedure using radical cyclization of the linear *S*,*O*-acetal and β-alkoxyacrylate.[74] After EE protection and removal of the TIPS group, hetero-Michael addition of the resulting alcohol with methyl propiolate provided β-alkoxyacrylate **294**. Treatment of **294** with *n*-Bu_3SnH and AIBN in toluene at 85 °C gave the desired G-ring oxepane **295**, which was then converted to the required RCM substrate **296** via two Wittig olefinations. The final critical RCM reaction of **296** for construction of the nine-membered F-ring

Scheme 22



Scheme 23



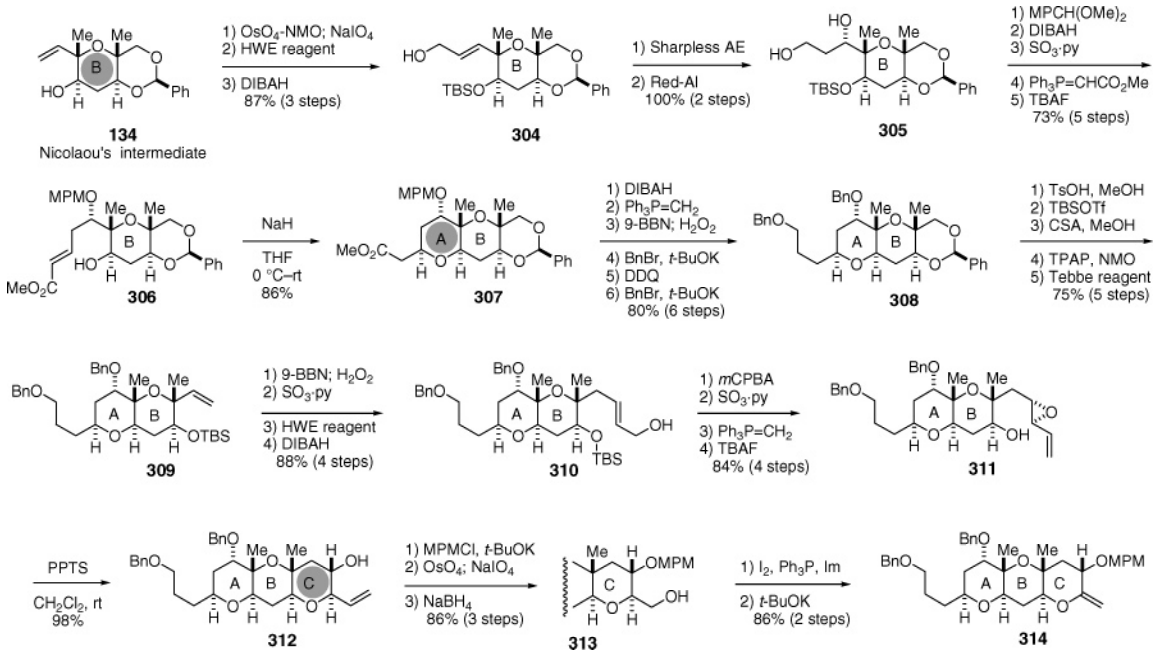
successfully proceeded using Grubbs catalyst **83** at 40 °C to afford the fully protected CTX3C (**297**) in 90% yield. The final deprotection of **297** was not a trivial step in Hirama's total synthesis. In their total synthesis, the three hydroxyl groups of CTX3C (**5**) were first protected as trisbenzyl ethers. LDBB reduction or oxidative cleavage with DDQ of the corresponding trisBn-CTX3C gave unsatisfactory results. Carefully controlled Birch reduction provided CTX3C (**5**) in only 7% yield. Thus, the benzyl protective groups were changed to the NAP groups as shown in this route. After considerable experiments, treatment of **297** with DDQ in aqueous CH_2Cl_2 furnished CTX3C (**5**) in 63% yield.

In 2004, Inoue, Hirama et al. reported the second-generation total synthesis based on direct construction of the *S*,*O*-acetal **300** by coupling of secondary alcohol **298** and α-chlorosulfide **299** (Scheme 23).[67d] The chlorosulfide **299** was prepared from aldehyde **291** by $NaBH_4$ reduction, introduction of phenyl sulfide, and installation of α-chloride with NCS. The coupling between **298** and **299** was achieved by treatment with AgOTf in the presence of DTBMP to give **300** in 70% yield. Removal of the TIPS group followed by treatment with methyl propiolate afforded β-alkoxyacrylate **301**. Radical cyclization of **301** with *n*-Bu_3SnH in the presence of AIBN constructed the desired G-ring **302** in 54% yield along with byproduct **303** (27%). DIBAH reduction of **302** followed by Wittig olefination afforded olefin **296**, whose RCM reaction and global deprotection already provided CTX3C (**5**) as shown in Scheme 22.

6. Total Synthesis of Gambierol

In 1993, Yasumoto and co-workers reported the isolation of gambierol (**6**) from cultures cells of the ciguatera causative dinoflagellate, *Gambierdiscus toxicus*.[75] The relative and absolute structure of **6** was established by extensive NMR studies and by an application of a chiral anisotropic reagent. The structure consists of trans-fused six-,six-,six-,six-, seven-,six-,six-,seven-membered octacyclic ether core (ABCDEFGH-ring) containing 18 chiral centers and a triene side chain including a conjugated (*Z,Z*)-diene system. Gambierol (**6**) exhibits potent toxicity against

Scheme 24



mice (LD_{50} = 50 μg/kg), and its symptoms resemble those caused by ciguatoxins, the principal toxin that is a very widespread seafood poisoning.

The total syntheses of gambierol (**6**) have been accomplished based on the convergent strategy by the Sasaki,[9] Kadota–Yamamoto,[10] and Rainier[11] groups, independently.

6.1. Sasaki's Total Synthesis

In 2002, Sasaki et al. achieved the first total synthesis of gambierol (**6**).[9] The convergent synthesis features their developed *B*-alkyl Suzuki–Miyaura coupling strategy[76] for the union of the ABC- and EFGH-ring segments, radical reduction of cyclic *S*,*O*-acetal for the construction of the D-ring, and introduction of the triene side chain by $Pd(Ph_3)_4$/CuCl/LiCl-promoted Stille coupling (Figure 3).

6.1.1. Synthesis of the ABC-ring

The synthesis of the ABC-ring **314** started with Nicolaou's intermediate **134**[6] for total synthesis of BTX-B (**1**) (Scheme 24). The intermediate **134** was converted to allyl alcohol **304** via chain elongation using HWE reaction. The Sharpless AE of **304** followed by reductive epoxide opening with Red-Al stereoselectively provided diol **305**, which was converted to α,β-unsaturated ester **306** in straightforward steps. Treatment of **306** with NaH in THF induced an intramolecular hetero-Michael cyclization to give the A-ring **307** in 86% yield. Chain elongation led to dibenzyl ether **308**, which was converted to allyl alcohol **310** via **309** in nine steps. The C-ring was constructed by Nicolaou's procedure[23] using 6-*endo*-cyclization of hydroxy vinylepoxide. After stereoselective epoxidation with *m*CPBA, the resulting α-epoxide was converted to hydroxy vinylepoxide **311**. Treatment of **311** with PPTS effected the expected 6-*endo*-cyclization to give the C-ring **312** in 98% yield, which was transformed to the desired *exo*-olefin **314**, corresponding to the ABC-ring, via **313** in straightforward steps.

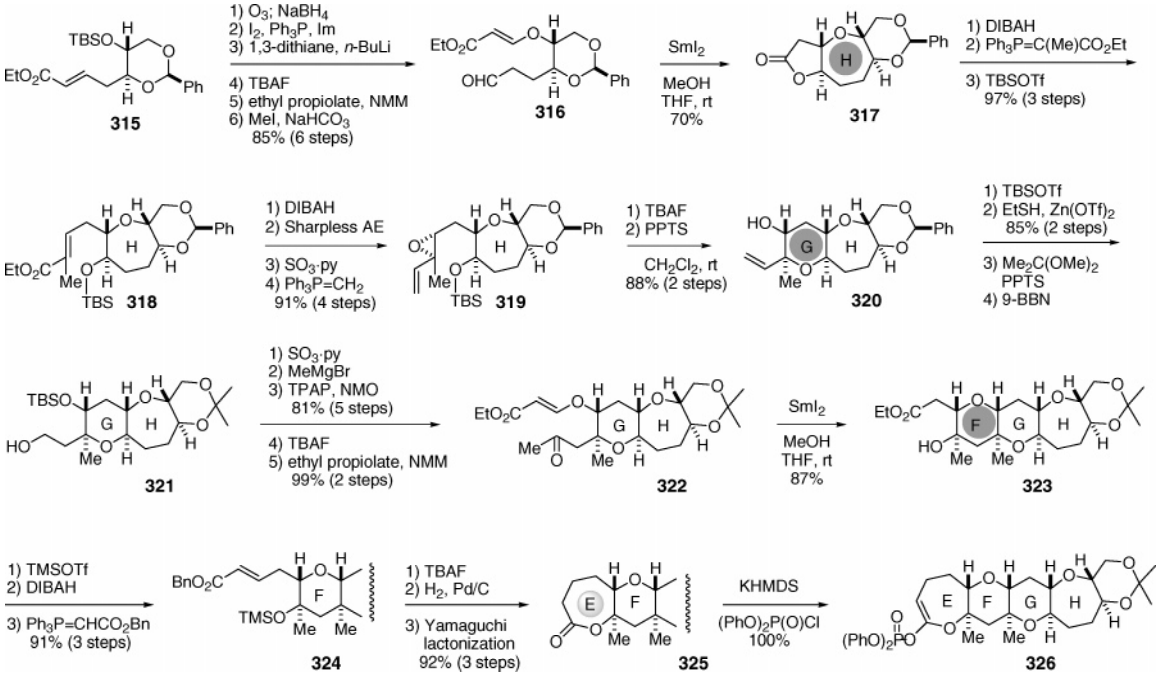
6.1.2. Synthesis of the EFGH-ring

The synthesis of the EFGH-ring **326** started with Nicolaou's intermediate **315**[7] for total synthesis of BTX-A (**2**) (Scheme 25). First, the H-ring was constructed by Nakata's protocol[57] using SmI_2-induced reductive cyclization. Aldehyde **316** was synthesized from **315** in six steps via hetero-Michael addition with ethyl propiolate. Reaction of **316** with SmI_2 effected reductive cyclization with concomitant lactonization to give the H-ring **317** in 70% yield with complete stereoselection. Then, the G-ring was constructed by Nicolaou's 6-*endo*-cyclization of hydroxy vinylepoxide.[23] The required vinylepoxide **319** was stereoselectively synthesized via ester **318** through Wittig reaction, Sharpless AE, and Wittig methylenation. After removal of the TBS group, treatment of **319** with PPTS effected 6-*endo*-cyclization to give the G-ring **320** in 88% yield. The construction of the F-ring was again completed by SmI_2-induced cyclization.[57] Functional group manipulation of **320** including Grignard methylation and hetero-Michael addition with ethyl propiolate provided methyl ketone **322** via **321**. SmI_2-induced cyclization of **322** effectively took place to give the F-ring **323** in 87% yield. Chain elongation of **323** and Yamaguchi's lactonization[27] afforded seven-membered lactone **325**. Treatment of **325** with KHMDS and $(PhO)_2P(O)Cl$ afforded cyclic enol phosphate **326**, corresponding to the EFGH-ring, as the other coupling partner.

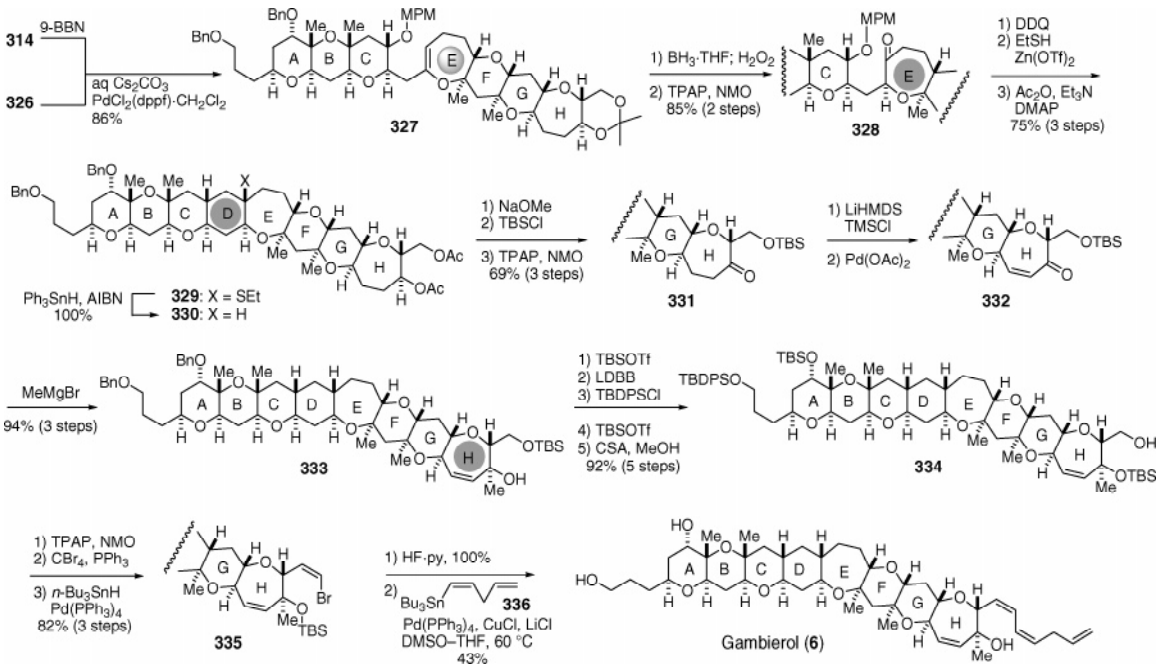
6.1.3. Completion of the Total Synthesis

The union of both segments **314** and **326** was accomplished by their developed strategy[76] based on *B*-alkyl Suzuki–Miyaura coupling (Scheme 26). Treatment of **314** with 9-BBN followed by addition of **326** in the presence of Cs_2CO_3 and $PdCl_2(dppf)\cdot CH_2Cl_2$

Scheme 25

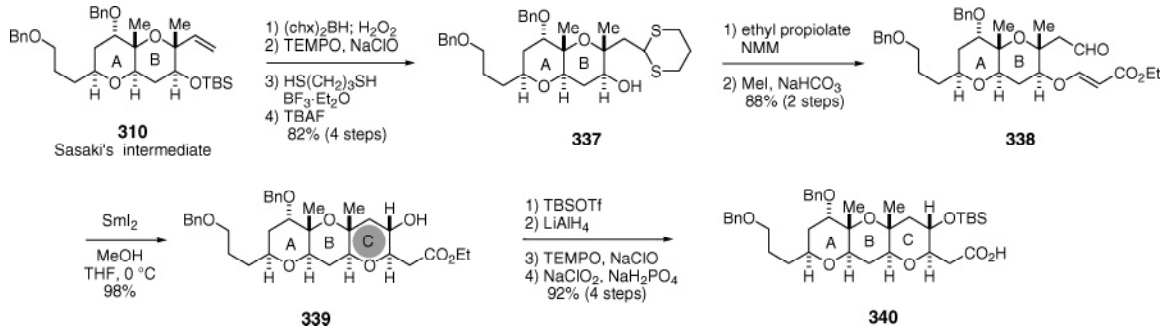


Scheme 26

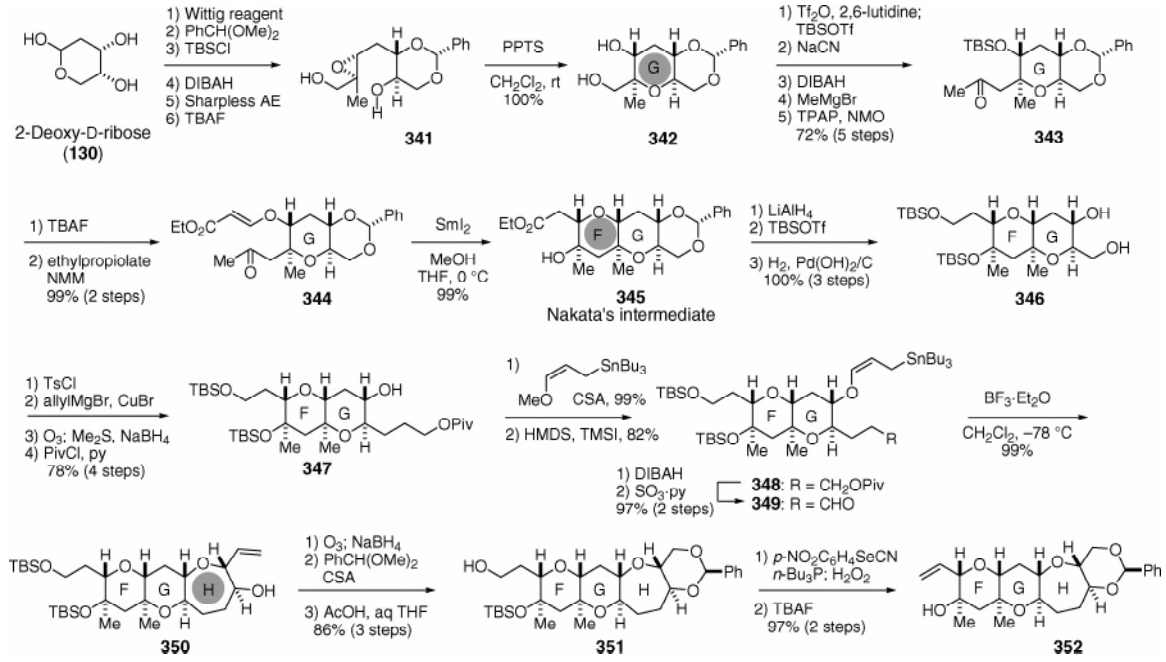


afforded cyclic enol ether **327** in 86% yield. Hydroboration followed by TPAP−NMO oxidation provided the E-ring ketone **328**. After removal of the MPM group, EtSH−$Zn(OTf)_2$ treatment simultaneously induced cyclic *S*,*O*-acetal formation and removal of the acetonide to give **329** after acetylation. Radical reduction of **329** with Ph_3SnH in the presence of AIBN constructed the D-ring **330**. Methanolysis of the diacetate in **330**, selective TBS protection, and TPAP−NMO oxidation afforded ketone **331**, which was converted to α,β-unsaturated ketone **332** using Saegusa procedure[77] by treatment with LiHMDS/TMSCl and then $Pd(OAc)_2$. A methyl group in the H-ring was stereoselectively introduced by treatment with MeMgBr to give **333** in 94% yield from **331**. The benzyl-TBS ether **333** was transformed to alcohol **334** by selective protective group manipulation. The construction of the triene side chain was accomplished by a modified Stille coupling protocol, which was originally reported by the Kadota−Yamamoto group.[78] After oxidation of the alcohol **334**, the resulting aldehyde was treated with CBr_4−Ph_3P and then *n*-Bu_3SnH−$Pd(PPh_3)_4$[79] to give vinylbromide **335**. The Stille coupling of **335** with vinylstannane reagent **336** was realized under Sasaki's optimal conditions, $Pd(PPh_3)_4$/CuCl/LiCl in DMSO−THF, to give the silyl-protected gambierol. However, global silyl ether deprotection for completion of the total synthesis was problematic. After extensive experimentation, it was found that the silyl groups of **335**

Scheme 27



Scheme 28



were completely removed by treatment with excess HF·pyridine. Finally, Stille coupling of the resulting triol with vinylstannane **336** under $Pd(PPh_3)_4$/CuCl/LiCl-promoted conditions effected stereoselective introduction of the side chain to furnish gambierol (**6**).

6.2. Kadota–Yamamoto's Total Synthesis

Kadota, Yamamoto, and co-workers have accomplished the second total synthesis of gambierol (**6**).[10] They developed a convergent strategy for the construction of polycyclic ethers based on intramolecular cyclization between γ-alkoxyallylstannane and α-acetoxy ether followed by RCM reaction.[80] The present strategy was applied to the union of the ABC- and FGH-rings, and consecutive construction of the D- and E-ring systems (Figure 3).

6.2.1. Synthesis of the ABC-ring

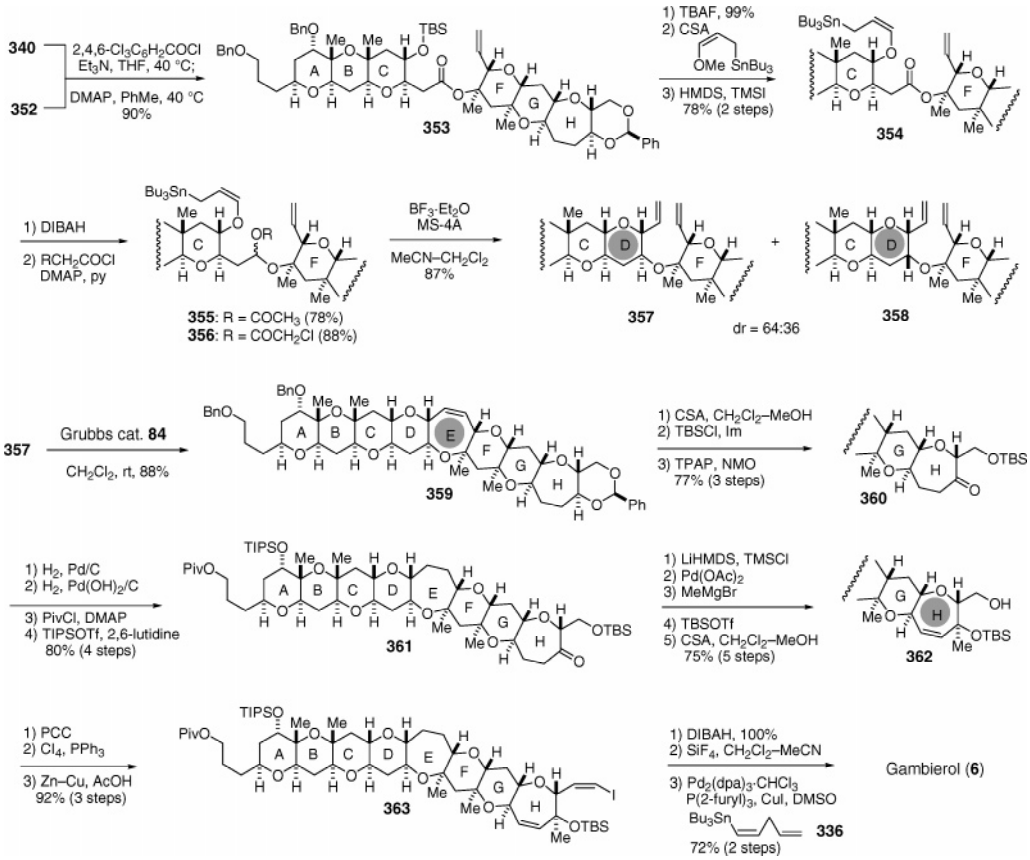
The synthesis of the ABC-ring system **340** started with Sasaki's intermediate **310**, corresponding to the AB-ring (Scheme 27). The required C-ring was constructed by Nakata's protocol[57] using SmI_2-induced reductive cyclization. The intermediate **310** was converted to the required β-alkoxyacrylate **338** in straightforward steps including hydroboration of **310** and hetero-Michael addition of **337** with ethyl propiolate. Treatment of **338** with SmI_2 in the presence of MeOH induced stereoselective reductive cyclization to give the ABC-ring **339** in 98% yield, which was converted to carboxylic acid **340** in four steps.

6.2.2. Synthesis of the FGH-ring

The synthesis of the FGH-ring **352** started with Nakata's intermediate **345**,[81] corresponding to the FG-ring, for their synthetic study of gambierol (Scheme 28). Nakata et al. synthesized the intermediate **345** based on 6-*endo*-cyclization of methylepoxide[60] and SmI_2-induced reductive cyclization.[57] Thus, treatment of methylepoxide **341**, prepared from 2-deoxy-D-ribose (**130**), with PPTS induced 6-*endo*-cyclization to give the G-ring **342** quantitatively. After conversion of **342** to methyl ketone **343**, desilylation followed by hetero-Michael addition with ethyl propiolate provided β-alkoxyacrylate **344**. Treatment of **344** with SmI_2 effectively induced stereoselective cyclization to give the F-ring **345** (99%) having 1,3-diaxial methyl groups.

Kadota et al. converted the ester **345** to the desired γ-alkoxyallylstannane **349** as a key substrate for the construction of the H-ring. Functional group manipulation of **345** including chain elongation provided alcohol **347** via diol **346**. Acid-catalyzed mixed acetal

Scheme 29



formation of **347** with γ-methoxyallylstannane followed by acetal cleavage with TMSI−HMDS afforded allylstannane **348**, which was converted to the required aldehyde **349**. BF_3·Et_2O-mediated intramolecular cyclization of **349** stereoselectively gave the H-ring oxepane **350** in 99% yield as a single stereoisomer. Subsequent ozonolysis of **350** followed by $NaBH_4$ reduction, benzylidene acetalization, and selective desilylation afforded **351**. *p*-Nitrophenylselenation followed by oxidative work up led to alkene, which was desilylated to give the FGH-ring segment **352**.

6.2.3. Completion of the Total Synthesis

With two segments **340** and **352** in hand, the stage was now set for completion of the total synthesis through their developed convergent strategy (Scheme 29). The carboxylic acid **340** and alcohol **352** were connected under Yamaguchi's conditions to give ester **353**. Desilylation with TBAF, acid-catalyzed acetal formation with γ-methoxyallylstannane, and acetal cleavage with TMSI−HMDS provided β-alkoxyallylstannane **354**. Rychnovsky's protocol[82] was applied to conversion of **354** to the α-acetoxy ether **355**; partial reduction of **354** with DIBAH followed by acetylation afforded α-acetoxy ether **355**. Treatment of **355** with BF_3·Et_2O in MeCN−CH_2Cl_2 provided the desired **357** and isomeric **358** in a ratio of 36:64 (61% yield). The stereoselectivity and yield were improved using the corresponding α-chloroacetoxy ether **356** to give the desired **357** and **358** in a ratio of 64:36 (87% yield). RCM reaction of **357** with Grubbs catalyst **84** gave the E-ring **359** (88% yield), which was transformed to ketone **361** via **360**. Construction of fully functionalized H-ring **362** was performed from **361** by following Sasaki's route. An efficient method for the construction of the triene side chain was developed via a modified Stille coupling of (*Z*)-iodoalkene **363** and (*Z*)-vinylstannane **336**. PCC oxidation of **362** followed by treatment with CI_4 and PPh_3 gave diiodoalkene, which was subjected to hydrogenolysis using a Zn−Cu couple in AcOH to afford (*Z*)-iodoalkene **363**. The protective groups were removed before coupling with (*Z*)-vinylstannane **336** as shown in Sasaki's route. After deprotection of the pivaloyl group with DIBAH and silyl groups with SiF_4, the resulting iodoalkene was subjected to the modified Stille coupling with **336** under $Pd_2(dba)_3$·$CHCl_3$/P(2-furyl)$_3$/CuI-promoted conditions to give gambierol (**6**).

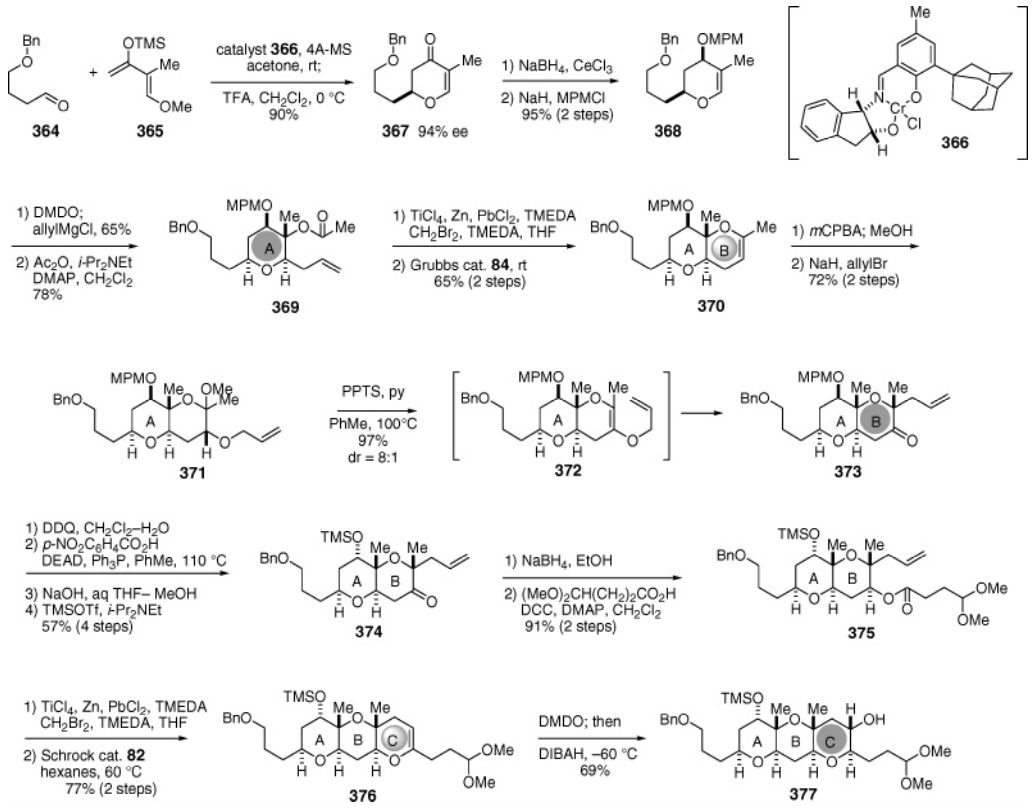
6.3. Rainier's Total Synthesis

Rainier et al. have accomplished convergent total synthesis of gambierol (**6**),[11] in which an iterative *C*-glycoside/enol ether−olefin RCM was efficiently used for the construction of each ether ring.

6.3.1. Synthesis of the ABC-ring

The construction of the ABC-ring system **377** started with the synthesis of tetrahydropyran as the A-ring (Scheme 30).[41c] The hetero-Diels−Alder cycloaddition of aldehyde **364** and Danishefsky's diene **365** was performed using Jacobsen's tridentate Cr(III) catalyst **366**[83] to give cycloadduct **367** in 90% yield with 94% ee. Luche reduction of the ketone **367**

Scheme 30



followed by MPM protection gave **368**. Epoxidation of **368** with DMDO followed by addition of allyl-MgCl afforded **369**, corresponding to the A-ring, after acetylation. The B-ring was constructed by an enol ether−olefin RCM. After conversion of the acetate **369** to acyclic enol ether using Takai's procedure,[43] RCM with Grubbs catalyst **84** smoothly proceeded at room temperature to give cyclic enol ether **370** in 65% yield. The next task was the construction of the B-ring having 1,3-diaxilal angular methyl groups. Unfortunately, the same strategy as that used for the A-ring construction, epoxidation followed by addition of allyl nucleophile, gave unsatisfactory results. However, this problem was overcome by Claisen rearrangement of allyl enol ether. Treatment of **370** with *m*CPBA in MeOH gave a 2:1 anomeric mixture of hydroxy acetal, which led to allyl ether **371**. Upon treatment of **371** with PPTS and pyridine in toluene at 100 °C, Claisen rearrangement took place through allyl enol ether intermediate **372** to give an 8:1 mixture of *C*-glycoside **373** with the desired stereochemistry and its epimer in 97% yield. The β-hydroxyl group on the A-ring was then inverted to an α-hydroxyl group; removal of MPM group in **373** followed by a modified Mitsunobu reaction[84] gave **374** having the desired α-stereochemistry, after hydrolysis and TMS protection. Reduction of **374** with $NaBH_4$ gave the desired equatorial β-alcohol, which was connected with $(MeO)_2CH(CH_2)_2CO_2H$ to give ester **375** as RCM precursor. The synthesis of acyclic enol ether using Takai's protocol followed by enol ether−olefin RCM with Schrock catalyst **82** gave tricyclic enol ether **376** in 77% yield. Then, construction of the functionalized C-ring with the desired stereochemistry was carried out. Epoxidation of **376** with DMDO followed by DIBAH reduction provided the desired alcohol **377** (69%), corresponding to the ABC-ring, through intramolecular delivery of hydride to oxocarbenium ion.

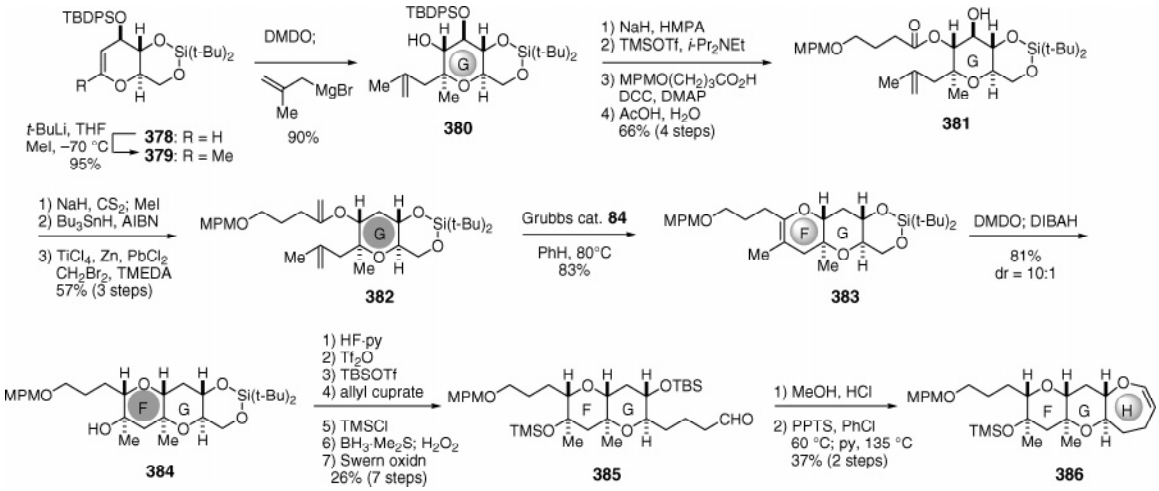
6.3.2. Synthesis of the FGH-ring

The construction of the FGH-ring system **386** was also performed using the same strategy used in the synthesis of ABC-ring segment **377** (Scheme 31).[85] The synthesis of the FGH-ring segment **386** started with D-glucal derivative **378**,[86] which was methylated with *t*-BuLi and MeI to give **379**. Treatment of **379** with DMDO followed by addition of 2-methylpropenyl-MgBr effected stereoselective epoxidation and addition of alkyl group to give **380** in 90% yield with >95:5 dr. Selective removal of the TBDPS group, selective TMS protection, esterification with MPMO-$(CH_2)_3CO_2H$, and removal of the TMS group afforded **381**. After removal of the hydroxyl group, **381** was converted to acyclic enol ether **382** using the Takai procedure. RCM of **382** with Grubbs catalyst **84** provided cyclic enol ether **383** in 83% yield. Epoxidation of **383** with DMDO followed by DIBAH reduction provided the desired **384** with 1,3-diaxial angular methyl groups as a 10:1 mixture of diasteromers in 81% yield. The FG-ring **384** was transformed to aldehyde **385** via chain elongation. Cyclic acetalization followed by removal of MeOH afforded the FGH-ring **386**.

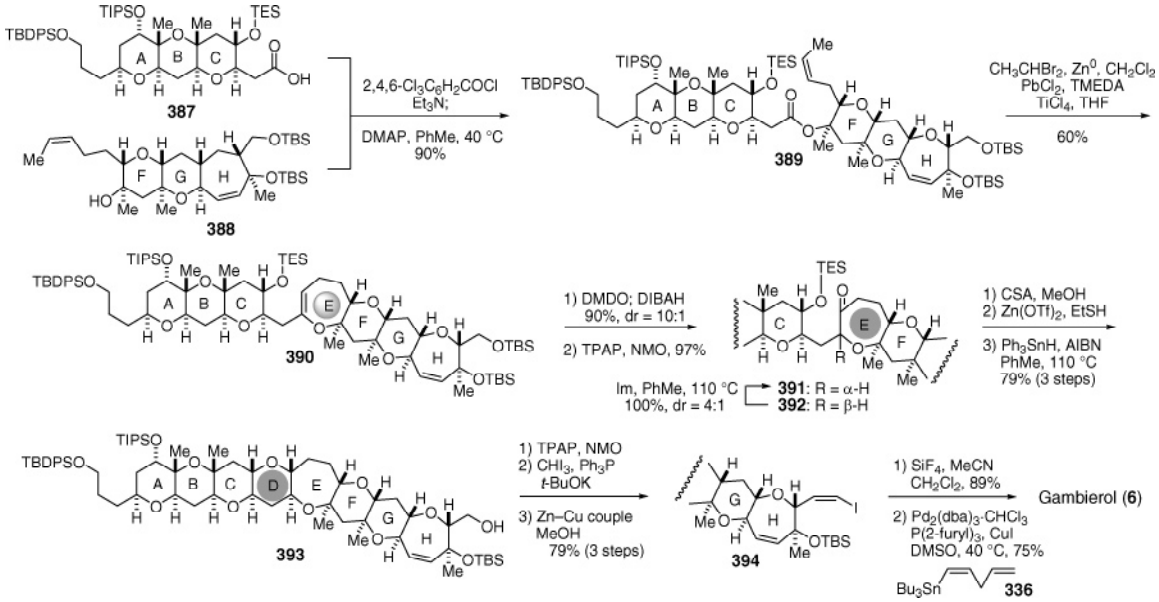
6.3.3. Completion of the Total Synthesis

The coupling of **387** and **388**, prepared on the basis of the above route, was carried out under Yamaguchi's conditions to give ester **389** (Scheme 32). After

Scheme 31



Scheme 32



many trials for the construction of the E-ring by RCM, they found the effective conditions for the cyclization. Reaction of **389** with the titanium alkylidene from 1,1-dibromoethane provided cyclic enol ether **390** in 60% yield. One-pot DMDO oxidation of **390** and DIBAH reduction afforded a separable 10:1 mixture of alcohols, which was oxidized with TPAP−NMO to give diastereomeric ketones **391** and **392**. Equilibration of the minor isomer **392** with imidazole in toluene at 110 °C produced a 4:1 mixture of the desired isomer **391** and **392**. After removal of the TES and primary TBS groups, *S*,*O*-acetal formation of **391** by treatment with EtSH−$Zn(OTf)_2$ followed by radical reduction with Ph_3SnH-AIBN constructed the D-ring to give **393**, corresponding to the ABCDEFGH-ring. Final introduction of triene side chain was carried out via **394** by Kadota−Yamamoto's and Sasaki's protocols to give gambierol (**6**).

7. Total Synthesis of Gymnocin-A

In 2002, Satake and co-workers reported the isolation of gymnocin-A (**7**) from the notorious red tide dinoflagellate *Karenia mikimotoi*.[87] The relative and absolute structure of gymnocin-A (**7**) was elucidated by a combination of extensive 2D-NMR analysis, FAB-collision-induced dissociation MS/MS experiments, and modified Mosher's method. The structure consists of a trans-fused five-,seven-,six-,seven-,six-,six-,seven-,six-,six-,six-,six-,seven-,six-,six-membered tetradecacyclic ether core (ABCDEFGHIJKLMN-ring) containing 31 chiral centers, γ-lactone, and a 2-methyl-2-butanal side chain. Gymnocin-A (**7**) exhibits in vitro cytotoxicity against P 388 murine leukemia cells (EC_{50} = 1.3 μg/mL).

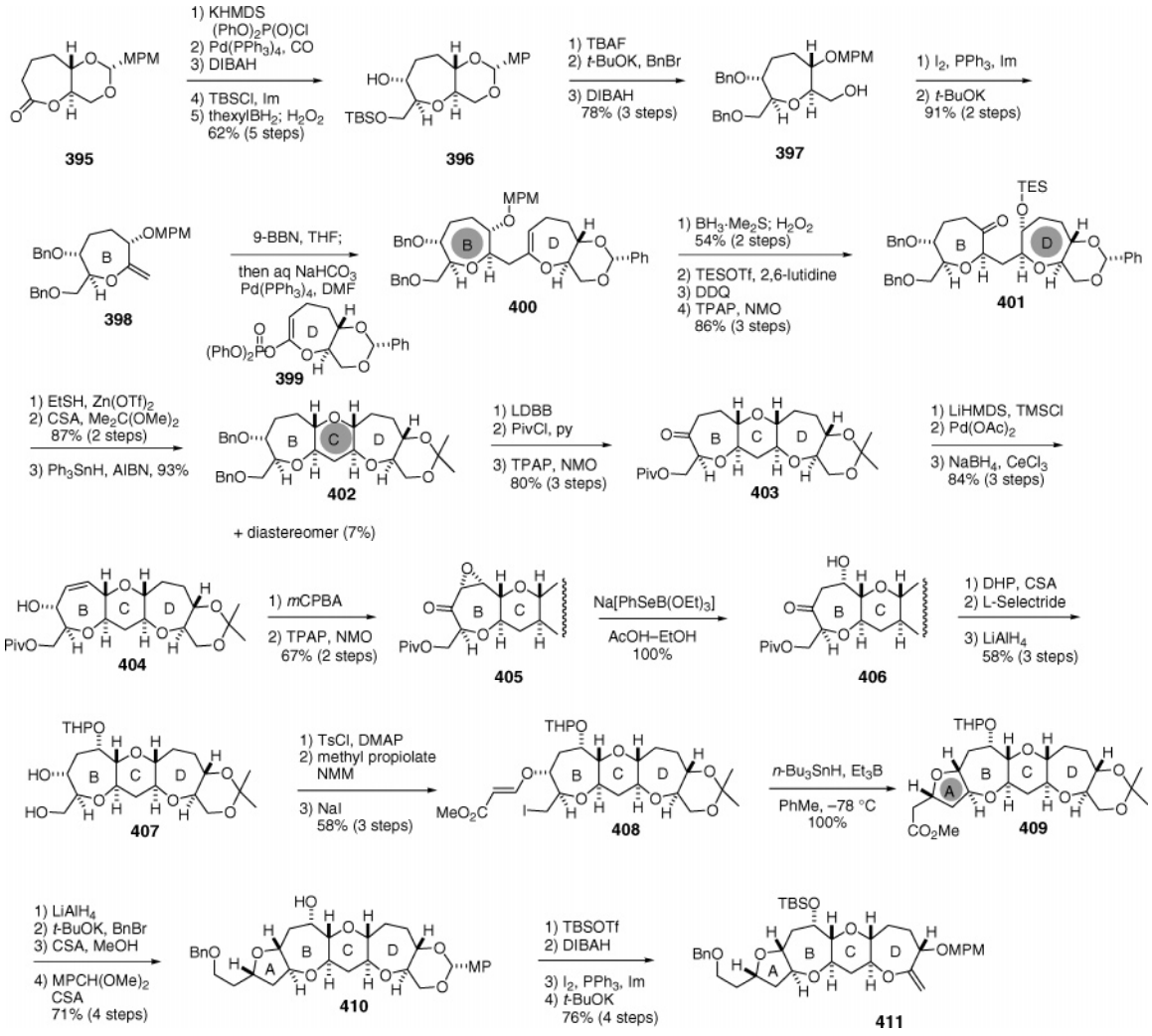
Recently, Sasaki et al. have achieved the first total synthesis of gymnocin-A (**7**) based on their developed *B*-alkyl Suzuki−Miyaura coupling strategy, demonstrating the usefulness and generality to the synthesis of marine polycyclic ethers (Figure 3).[13]

7.1. Sasaki's Total Synthesis

7.1.1. Synthesis of the ABCD-ring

The synthesis of the ABCD-ring system **411** was achieved based on the *B*-alkyl Suzuki−Miyaura coupling strategy and radical cyclization for the

Scheme 33



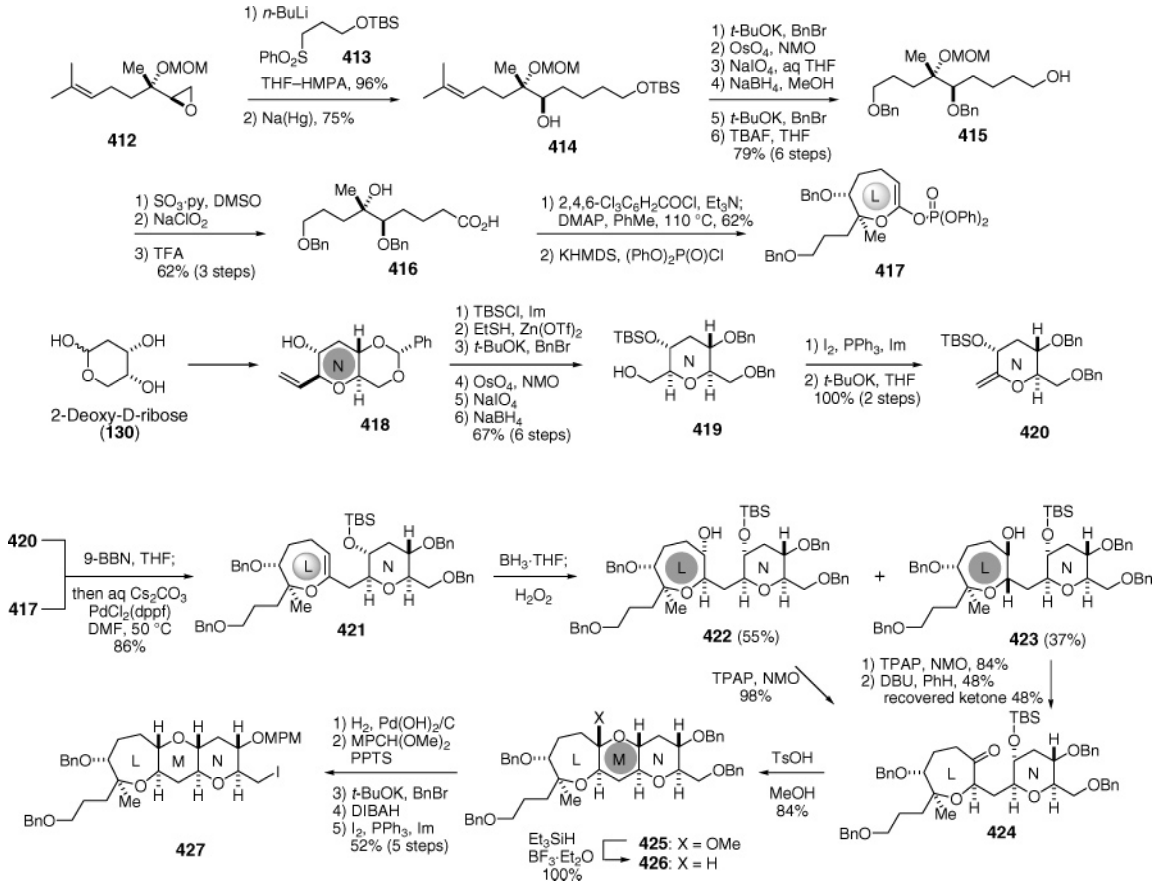
construction of the A-ring (Scheme 33).[88] The seven-membered lactone **395** was converted to alcohol **396** through Pd(0)-mediated carbonylation of the corresponding enol phosphate, and hydroboration of cyclic enol ether.[89] Standard functional group manipulation led to *exo*-cyclic enol ether **398** via **397**. The *B*-alkyl Suzuki−Miyaura coupling reaction of an alkylborane, generated from **398**, with the enol phosphate **399** by treatment with aqueous $NaHCO_3$ and $Pd(PPh_3)_4$ in DMF afforded the desired **400**. Subsequent hydroboration of **400**, TES protection, removal of MPM group, and TPAP oxidation provided ketone **401**. Treatment of **401** with EtSH−$Zn(OTf)_2$ simultaneously induced removal of the TES and benzylidene acetal groups, and cyclization to *S*,*O*-acetal, which after acetonide protection was subjected to radical reduction to give the tricyclic BCD-ring **402**. After conversion of **402** to ketone **403**, Saegusa's protocol afforded enone, which was subjected to Luche reduction to give α-alcohol **404**. The stereoselective epoxidation of **404** with *m*CPBA followed by TPAP oxidation afforded α,β-epoxy ketone **405**. The Miyashita reduction[90] of **405** with Na[PhSeB(OEt)$_3$] afforded the desired β-hydroxy ketone **406**. After protection of **406** as its THP ether, L-Selectride reduction followed by $LiAlH_4$ reduction stereoselectively provided diol **407**, which was transformed to iodo β-alkoxyacrylate **408**. Treatment of **408** with *n*-Bu_3SnH in the presence of Et_3B effected cyclization to give the A-ring **409** as a single product. The ABCD-ring **409** was then converted to *exo*-cyclic enol ether **411** via **410** by functional group manipulation.

7.1.2. Synthesis of the FGHIJKLMN-ring

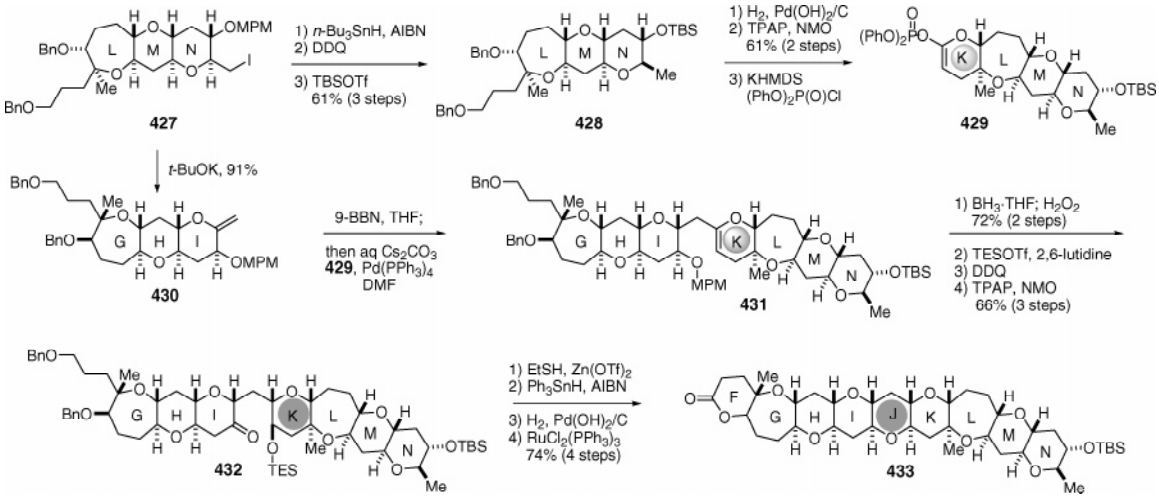
The FGHIJKLMN-ring system **433** was constructed by convergent union of the GHI- and KLMN-rings, **430** and **429**, both of which were synthesized from a common precursor, **427** (Schemes 34 and 35).[91] The key intermediate **427** was prepared by coupling of monocyclic ethers **417** and **420** (Scheme 34).

The synthesis of *endo*-cyclic enol phosphate **417**, an L-ring precursor, started with the known epoxide **412**,[92] derived from geraniol (Scheme 34). Addition of sulfone **413** to the epoxide **412** followed by Na(Hg) reduction afforded alcohol **414**, which was converted to carboxylic acid **416** by functional and protective group manipulations. Lactonization under Yamaguchi's conditions and treatment with KHMDS/$(PhO)_2P(O)Cl$ afforded the desired enol phosphate **417**. On the other hand, the synthesis of *exo*-cyclic enol ether **420**, an N-ring precursor, started with **418**,[76c] which was prepared from 2-deoxy-D-ribose (**130**) by following Nicolaou's *endo*-cyclization of vinylepoxide. The

Scheme 34



Scheme 35

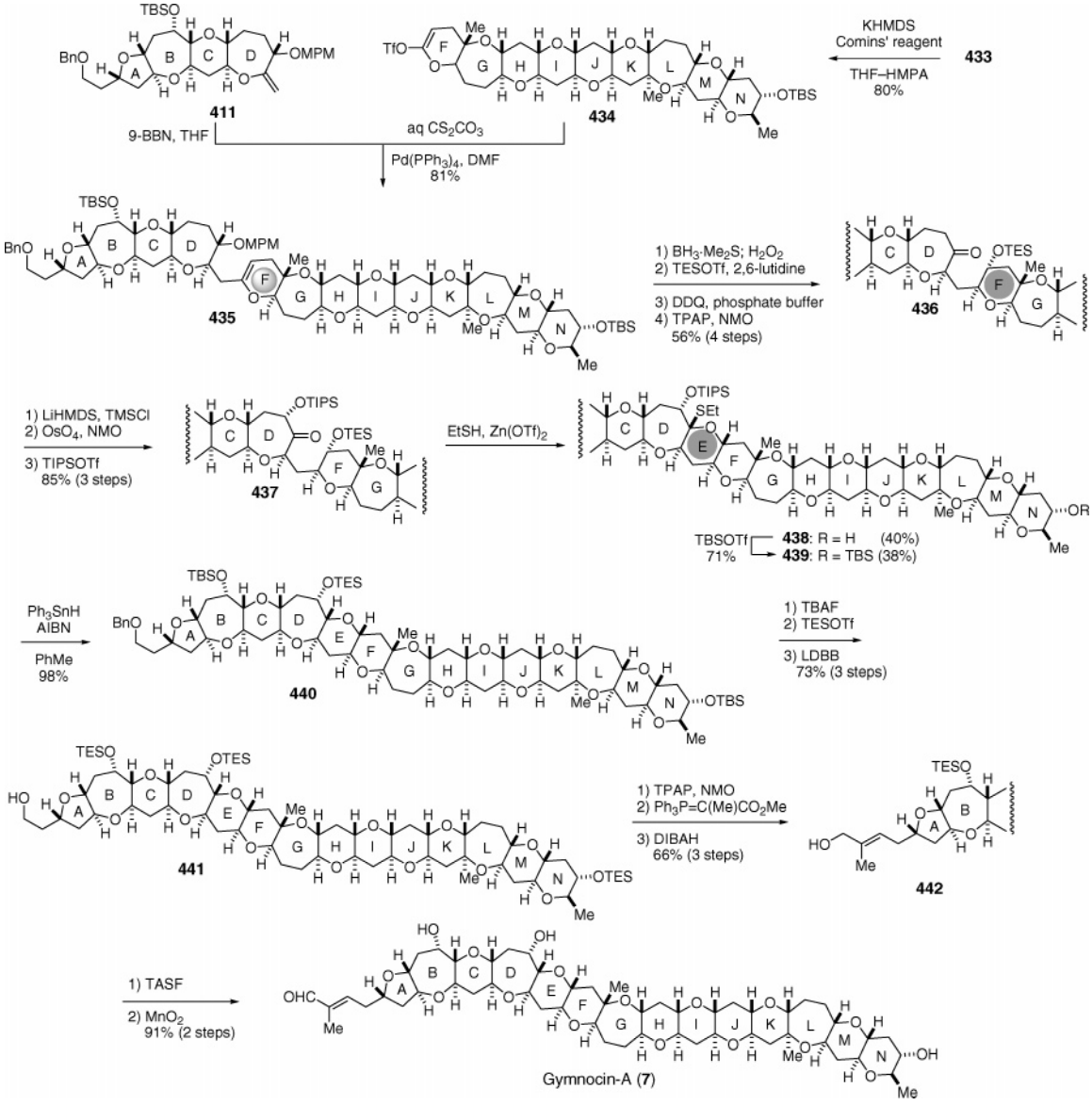


protective and functional group manipulations led to alcohol **419**, which was subjected to iodination and *t*-BuOK treatment to give the desired *exo*-cyclic ether **420**.

The common intermediate **427** for the GHI- and LMN-rings was synthesized by coupling of **417** and **420** (Scheme 34). The Suzuki−Miyaura coupling of an alkylborane, prepared from **420** with 9-BBN, and **417** by treatment with aqueous Cs_2CO_3 and $PdCl_2$-(dppf) in DMF at 50 °C afforded the desired *endo*-cyclic enol ether **421** in 86% yield. Subsequent hydroboration of **421** with BH_3·THF afforded a separable mixture of the desired **422** (55%) and the diastereomer **423** (37%). Oxidation of **422** with TPAP−NMO afforded ketone **424**. The undesired diastereomer **423** was also converted to the desired **424** by TPAP−NMO oxidation followed by epimerization with DBU treatment. Acid treatment of **424** followed by LA-mediated reduction of cyclic acetal **425** gave the LMN-ring **426**, which was converted to LMN iodide **427** in a standard manner.

The iodide **427**, corresponding to both LMN- and GHI-rings, was converted to the KLMN-ring enol phosphate **429** and the GHI-ring *exo*-cyclic ether **430**, respectively, in a standard manner (Scheme 35). The *B*-alkyl Suzuki−Miyaura coupling reaction of the enol phosphate **429** with an alkylborane, generated from **430**, smoothly proceeded by treatment with

Scheme 36



aqueous Cs_2CO_3 and $Pd(PPh_3)_4$ in DMF to afford the desired **431** in good yield. Hydroboration of the K-ring stereoselectively afforded β-alcohol, which was subjected to TES protection, removal of the MPM group, and TPAP oxidation to give ketone **432**. Treatment of **432** with EtSH−$Zn(OTf)_2$ afforded the cyclic *S*,*O*-acetal, which was reduced by Ph_3SnH-AIBN to construct the J-ring, hydrogenated to remove benzyl protective groups, and oxidized by $RuCl_2(PPh_3)_3$ to lactone **433**, corresponding to the FGHIJKLMN-ring.

7.1.3. Completion of the Total Synthesis

The total synthesis of gymnocin-A (**7**) has been accomplished through union of the ABCD- and FGHIJKMN-rings, **411** and **434** (Scheme 36).

The enol triflate **434**, as the coupling partner, was prepared from the FGHIJKLMN-ring **433** by successive treatment with KHMDS and then Comins' reagent.[93] The Suzuki−Miyaura coupling of the alkylborane, derived from the *exo*-cyclic enol ether **411**, with **434** provided the cross-coupling product **435** in 81% yield. Hydroboration of **435** with BH_3·Me_2S followed by TES protection stereoseletively afforded α-TES ether, which was subjected to removal of the MPM group and TPAP oxidation to give ketone **436**. The introduction of the α-alcohol was performed through oxidation of silyl enol ether derived from **436**; successive treatment of **436** with LiHMDS-TMSCl, OsO_4-NMO, and TIPSOTf stereoselectively afforded α-hydroxylated ketone **437**. Treatment with EtSH−$Zn(OTf)_2$ in $MeNO_2$ induced desilylaton and cyclization to give *S*,*O*-acetal **439** (38%) and its desilylated product **438** (40%). The latter product **438** was resilylated to give **439**. Reductive desulfulization of **439** with Ph_3SnH-AIBN provided the tetradecacyclic ether **440**, corresponding to the ABCDEFGHIJKLMN-ring. After protective group manipulation, the resulting alcohol **441** was converted to allyl alcohol **442** via TPAP-NMO oxidation, Wittig reaction, and DIBAH reduction. Finally, removal of the TES groups with TASF[94] followed by oxidation with MnO_2 furnished gymnocin-A (**7**).

8. Summary

Since the first isolation of BTX-B (**1**) in 1981, the unprecedented structure and potent bioactivity of marine polycyclic ethers have attracted much attention of numerous synthetic organic chemists. Their intensive endeavors have accumulated many efficient strategies and useful methods for construction of various types of polycyclic ether ring systems. Besides the landmark total syntheses of BTX-B (**1**) and A (**2**) by the Nicolaou group in 1995 and 1998, respectively, recent remarkable progress in synthetic organic chemistry has completed efficient syntheses of these marine polycyclic ethers, including BTX-B (**1**), CTX3C (**5**), gambierol (**6**), and gymnocin-A (**7**). Further challenge to the synthesis of marine polycyclic ethers including yessotoxin, ciguatoxin, and even MTX (**8**) will make great progress and contributions to organic chemistry, design of new bioactive compounds, and biological studies.

9. Abbreviations

acac	acetylacetonyl
AE	asymmetric epoxidation
AIBN	2,2′-azobisisobutyronitrile
aq	aqueous
9-BBN	9-borabicyclic[3.3.1]nonane
Bn	benzyl
ca.	circa (approximately)
cat.	catalyst
CBS	Corey−Bakshi−Shibata
chx	cyclohexyl
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAH	diisobutylaluminum hydride
DMAP	4-*N,N*-(dimethylamino)pyridine
DMDO	dimethyl dioxirane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
EE	1-ethoxyethyl
ee	enantiomeric excess
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HWE	Horner−Wadsworth−Emmons
i	iso
Im	imidazol-1-yl or imidazole
KHMDS	potassium hexamethyldisilazide
K−Selectride	potassium tri-*s*-butylborohydride
LA	Lewis acid
LDA	lithium diisopropylamide
LDBB	lithum 4,4′-*tert*-butylbiphenylide
LiHMDS	lithium hexamethyldisilazide
L-Selectride	lithium tri-*s*-butylborohydride
*m*CPBA	*m*-chloroperbenzoic acid
MOM	methoxymethyl
MP	*p*-methoxyphenyl
MPM	*p*-methoxyphenyl methyl
MS	molecular sieves
Ms	mesyl (methanesulfonyl)
n	normal
NaHMDS	sodium hexamethyldisilazide
NAP	2-naphthyl methyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
p	para
Piv	pivaloyl (trimethylacetyl)
PPTS	pyridinium *p*-toluenesulfonate
py	pyridine
RCM	ring-closing metathesis
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
s	secondary
sia	1,2-dimethylpropyl
t	tertiary
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy radical
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
Th	thienyl
thexyl	1,1,2-trimethylpropyl
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TIPS	triisopropylsilyl
TIPDS	tetra-*i*-propyldisiloxyl
TMEDA	*N,N,N′*,N′-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	*p*-tolyl
TPP	*meso*-tetraphenylporphyrin
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl (triphenylmethyl)
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid.

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