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A New Stereoselective Synthesis of Ciguatoxin Right Wing Fragments

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The right wings (**13** and **14**) of ciguatoxins were synthesized highly stereoselectively. Key transformations in the synthesis are (i) an oxiranyl anion strategy to attach the H ring, (ii) intramolecular carbonyl olefination to cyclize the J ring, (iii) regio- and stereoselective reduction of the epoxyacetal to install the C42-stereocenter, and (iv) stereoselective reductive etherification to construct the K ring. The present procedure greatly improved the stereoselectivity and efficiency in comparison to a previous synthesis. Remarkably, only 23 steps were required from monocyclic I ring **5** to construct the ciguatoxin right wings. The high practicality of the present synthesis ensures a sufficient supply of these complex fragments for total syntheses and biomedical applications.

Introduction

Ciguatera is a human intoxication caused by the ingestion of a variety of reef fish.[1] More than 20 000 victims suffer annually from ciguatera, making it one of the largest scale food poisoning of nonbacterial origin. Ciguatoxins are characterized as being principal causative toxins of this type of poisoning (Figure 1).[2] Upon ingestion, these toxins cause various disorders involving the neurological, gastrointestinal, and cardiovascular systems by means of the persistent activation of voltage-sensitive sodium channels.[3] Because the presence of these toxins in fish is unpredictable, a sensitive immunochemical method for detecting ciguatoxins has long been required.[4] In 1989, by applying state-of-the-art NMR techniques to minute amounts of samples, Yasumoto et al. successfully elucidated the structures of ciguatoxin CTX **4** and CTX4B **3**, which were found to be huge polycyclic ethers with the molecular lengths over 3 nm.[2a,b] In subsequent studies, they isolated other congeners including CTX3C **1**[2d] and 51-hydroxyCTX3C **2**.[2e] The right wings of structures **1** and **2** are the same as **3** and **4**, respectively, but the left wings of both **1** and **2** lack the side chain of **3**/**4** and have an eight-membered E ring instead of the seven-membered ring of **3**/**4**.

Motivated by the biological problems of these molecules and also their fascinating molecular architecture, we launched a program for the total synthesis of ciguatoxins and recently achieved the first practical total synthesis of CTX3C **1**.[5,6] The final stage of synthesis involved coupling between the left and right wings with subsequent construction of the central FG ring system.[5,7] Other ciguatoxin structural variants (**2**, **3**, and **4**) are regarded as important synthetic targets for their use in antibody preparation and a detailed structure−activity relationship (SAR) study. Importantly, the presented strategy for coupling the two halves of the molecule is applicable to all ciguatoxins because ciguatoxin congeners share the FG ring structure.[2] In this full account, we describe a significantly improved protocol (Scheme 1) for the concise and stereoselective synthesis of the protected ciguatoxin

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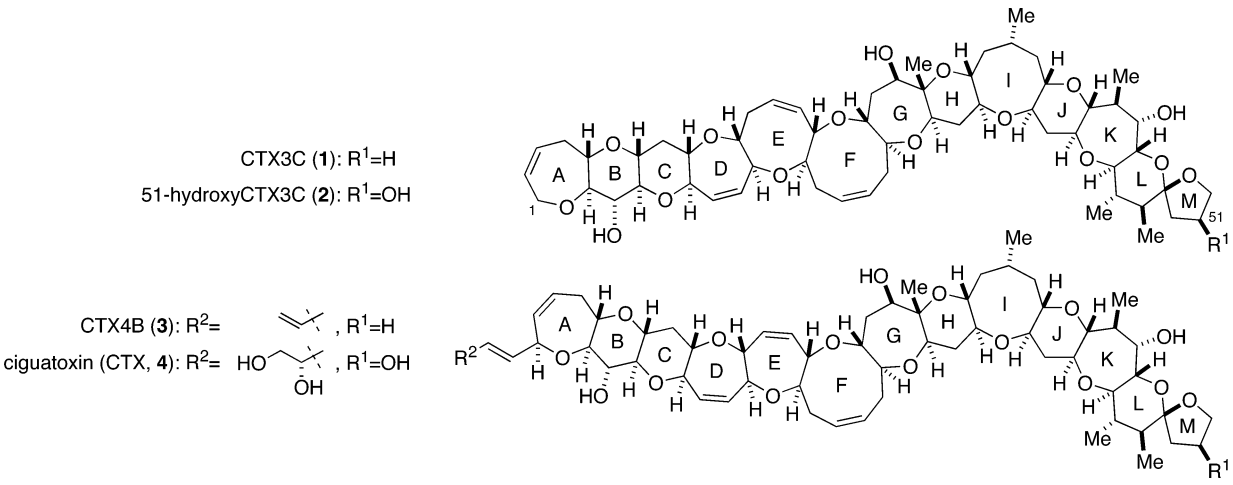
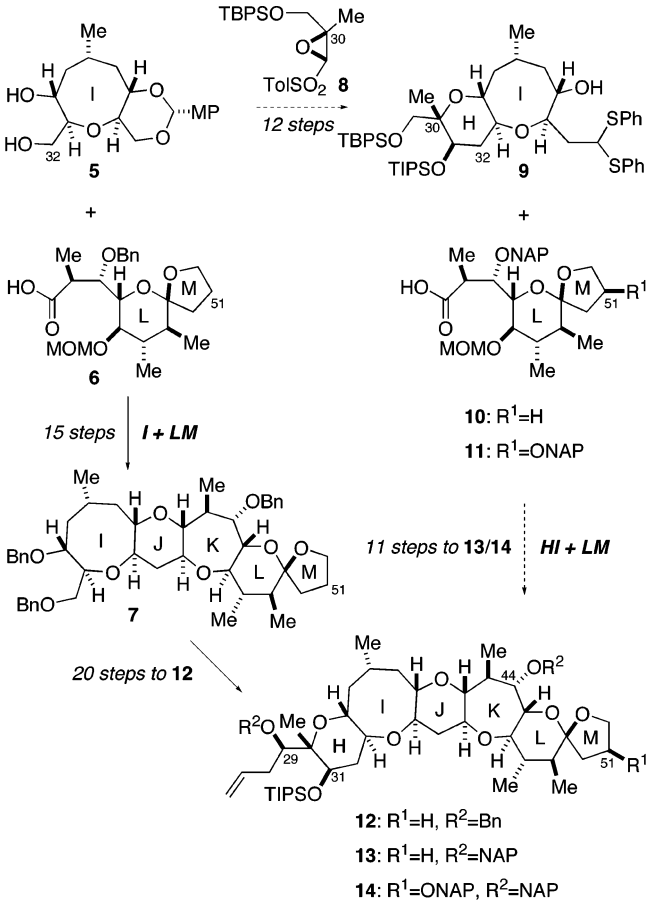


FIGURE 1. Structures of ciguatoxins.

SCHEME 1. New Synthetic Plan of the Right Wing of Ciguatoxins



right wings **13** and **14**. An available synthesis of these compounds enables the total syntheses of various ciguatoxins and the future preparation of antibodies. [8−10]

Results and Discussion

Synthetic Plan. In the previous synthesis of the right half of CTX3C (**12**, Scheme 1), the entire IJKLM ring segment **7** was constructed from the I (**5**) and LM (**6**) ring segments in a convergent manner by 15 separate transformations. However, the subsequent attachment of the H ring to **7** required 20 synthetic steps.[11] To avoid this cumbersome construction of the H ring, the four-carbon unit **8** corresponding to the H ring was to be directly introduced via the oxiranyl anion strategy developed by Mori.[12] Furthermore, it was planned that the H ring would be attached to the I ring fragment (**5** + **8** → **9**) instead of the IJKLM ring system **7** to maximize synthetic convergency and minimize protective group manipulations. After construction of the HI ring system **9**, **9** would be coupled with LM ring **10** or protected 51-hydroxyl LM ring **11** to produce the ciguatoxin right wings (**13** or **14** respectively). All alcohol groups except that of C31 were protected by NAP (2-naphthylmethyl) groups,[13] the utility of which was demonstrated in our improved total synthesis of CTX3C **1**.[5b]

Synthesis of LM Ring Fragments. Synthesis of the NAP-protected LM ring **10** of CTX3C (**1**) began with the previously reported olefin **15** (Scheme 2).[11,14,15] A hy-

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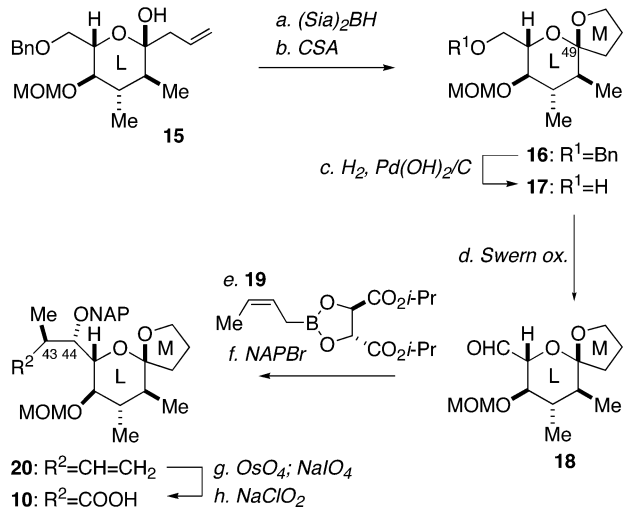
SCHEME 2. Synthesis of the LM Ring of CTX3C[a]



[a] Reagents and conditions: (a) $(Sia)_2BH$, THF, 0 °C, then $NaHCO_3$, H_2O_2; (b) CSA, $(CH_2Cl)_2$, rt, 75% (three steps); (c) H_2, $Pd(OH)_2/C$, EtOAc, rt, 100%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −80 to −60 °C; (e) **19**, toluene, −80 to −70 °C; (f) NAPBr, NaH, DMF, THF, rt, 52% (three steps); (g) OsO_4, NMO, *t*-BuOH/H_2O (1:1), rt, then $NaIO_4$, rt; (h) $NaClO_2$, $NaH_2PO_4 \cdot 2H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), rt, 99% (two steps).

droboration−oxidation sequence was carried out on the terminal olefin of **15** followed by acid treatment to afford the thermodynamically stable spiroacetal **16** as a single isomer in 75% overall yield. The liberation of the primary alcohol of **16** by hydrogenolysis and subsequent oxidation under Swern conditions led to aldehyde **18**.[11] Subsequent treatment of **18** with (*R*,*R*)-diisopropyl tartrate (*Z*)-crotylboronate **19**[16] resulted in stereoselective introduction of both the C43-methyl and C44-hydroxyl groups. After NAP protection of the newly formed secondary alcohol, **20** was isolated as a single isomer in 52% yield from **17**. Finally, oxidative cleavage of the olefin of **20** and subsequent oxidation provided carboxylic acid **10** quantitatively.

As illustrated in Scheme 3, the same starting material **15** was used for the synthesis of the 51-hydroxyl LM ring fragment **11**. After conversion of hemiacetal **15** to methyl acetal **21** (94%), the 51-OH group was installed by Sharpless asymmetric dihydroxylation using $(DHQ)_2PYR$ as a ligand,[17] yielding desired diol **23** as the major diastereomer (**23**/**22** = 4:1, 97% yield). Subsequent M ring formation of the isolated **23** under the conditions used to prepare **16** [CSA, $(CH_2Cl)_2$] exhibited little preference for the presumably thermodynamically more stable **25**β (**25**β/**25**α = 2:1). Thus, conditions for transacetalization using the undesired isomer **25**α were investigated (Table 1). Whereas CSA typically caused decomposition of the compound at high temperature, products **25**α and **25**β survived under PPTS treatment even at 80 °C. The ratio of the desired **25**β depended considerably on the solvent, and acetonitrile was found to be the best solvent of those studied (**25**β/**25**α = 8.5:1). Application of these modified conditions for the acetal formation step led directly to the selective formation of **25**β (85% yield, Scheme 3) in the same ratio (8.5:1). The isolated **25**α was again isomerized to obtain additional **25**β in 75% yield. The other Sharpless asymmetric dihydroxylation product, C51 epimer **22**, was subjected to transacetalization to selectively afford **24**β (**24**β/**24**α = 5:1). The C51 stereocenter of **24**β was then inverted under Mitsunobu conditions[18] to obtain **25**β in 91% yield after saponification of the benzoyl ester.[9i]

The secondary alcohol of spiroacetal **25**β was temporarily masked with TIPS in 96% yield, and the benzyl group was then removed by hydrogenolysis to provide primary alcohol **26**. After oxidation of **26**, addition of **19**[16] to aldehyde **27** created the two stereocenters (C43, C44), giving rise to **28** with complete stereochemical control (79% for three steps). Removal of the TIPS group from **28** and introduction of the NAP group produced bis-NAP ether **29** in 99% overall yield. Finally, oxidative cleavage of the terminal olefin of **29**, followed by oxidation to the carboxylic acid, led to the 51-hydroxyl LM ring fragment **11** in 82% yield for two steps.

Synthesis of HI Ring Fragment. The common coupling partner of **10** and **11**, HI ring fragment **9**, was efficiently prepared from the known I ring **5** using Mori's oxiranyl anion strategy (Scheme 4).[12] Diol **5**[11b] was converted to unstable triflate **30** by stepwise addition of Tf_2O and TESOTf in the presence of 2,6-lutidine and molecular sieves 4A. A mixture of the resultant **30** and epoxysulfone **8**[12d] in THF−HMPA was treated with *n*-BuLi at −110 °C for 30 min, leading to the formation of the desired coupling adduct **31**. At this stage, 6-endo cyclization to construct the H ring was realized by subjecting **31** to *p*-TsOH in $CHCl_3$ with *p*-methoxybenzaldehyde dimethyl acetal to afford fused ether **32** through concomitant removal of TES (51% from **5**). The presence of the dimethyl acetal in the reaction mixture was necessary for in situ reattachment of the MP acetal to partially deprotected **31** and/or **32**. The obtained **32** was stereoselectively reduced using $NaBH_4$, and the newly formed alcohol was protected as its TIPS ether to give **33** as the sole isomer in quantitative yield (two steps), thus completing five-step construction of the H ring from **5**. After acid-promoted removal of the MP acetal from **33**, one-carbon extension of **34** at the primary alcohol via iodination (87%) and displacement with cyanide (99%) led to **35**. TES protection of secondary alcohol **35** yielded **36** quantitatively. Nitrile **36** was reduced to the corresponding aldehyde, which was then converted to dithioacetal **37** using phenyl disulfide and PBu_3 (83% yield, two steps).[19] For the next coupling reaction, the TES group of the tris-silylated **37** was selectively removed using

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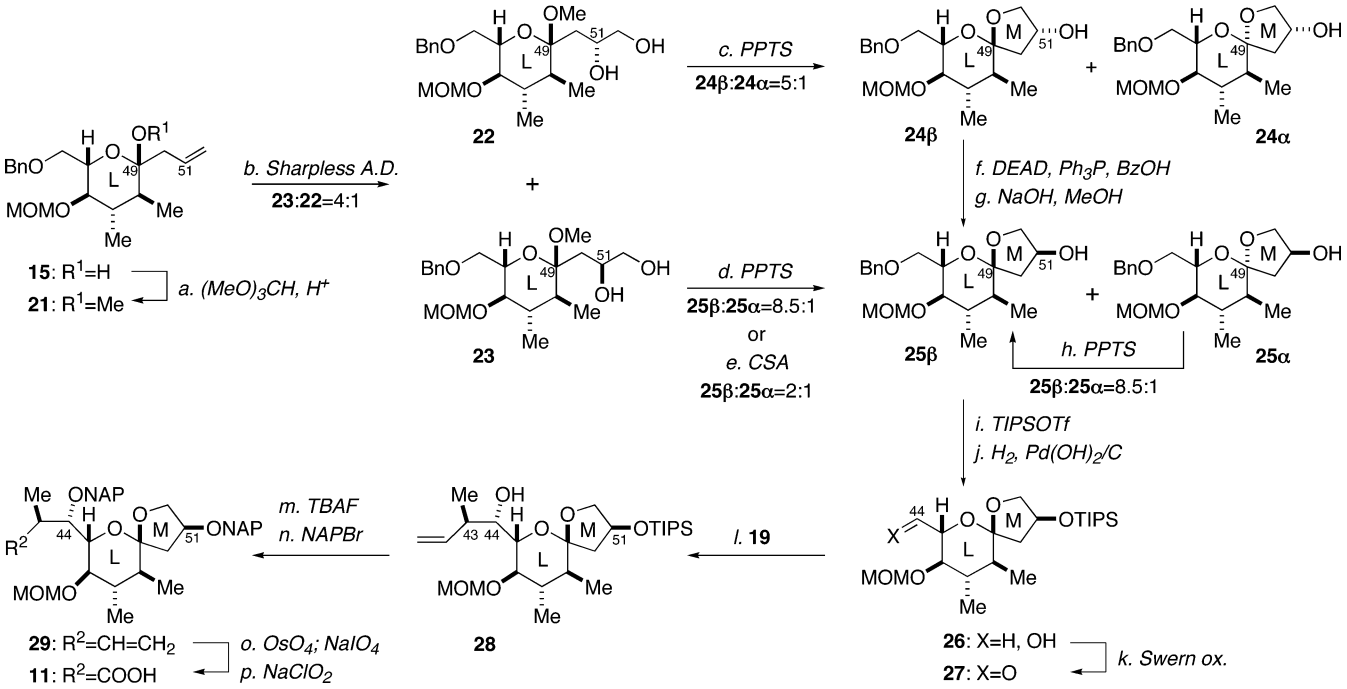
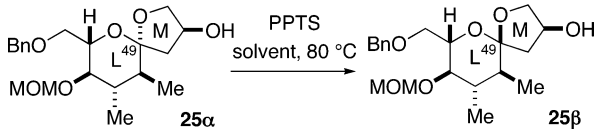
SCHEME 3. Synthesis of the LM Ring of 51-HydroxyCTX3C[a]



[a] Reagents and conditions: (a) $(MeO)_3CH$, CSA, $(CH_2Cl)_2$, rt, 99%; (b) OsO_4, $(DHQ)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O (1:1), 0 °C, **23**: 78%, **22**: 19%; (c) PPTS, MeCN, 80 °C, **24***β*: 75%, **24**α: 15%; (d) PPTS, MeCN, 80 °C, **25***β*: 85%, **25**α: 10%; (e) CSA, $(CH_2Cl)_2$, rt, **25***β*: 60%, **25**α: 30%; (f) DEAD, Ph_3P, BzOH, toluene, rt; (g) NaOH, MeOH, rt, 91% (two steps); (h) PPTS, MeCN, 80 °C, **25***β*: 75%, **25**α: 9%; (i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 96%; (j) H_2, $Pd(OH)_2$/C, EtOAc, rt; (k) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; (l) **19**, 4 Å MS, toluene, −78 °C, 79% (three steps); (m) TBAF, THF, rt; (n) NAPBr, TBAI, NaH, THF/DMF (3:1), 0 °C to rt, 99% (two steps); (o) OsO_4, NMO, *t*-BuOH/H_2O (1:1), rt, then $NaIO_4$; (p) $NaClO_2$, $NaH_2PO_4 \cdot H_2O$, 2-methyl-2-butene, *t*-BuOH/H_2O (4:1), 82% (two steps).

TABLE 1. Acetal Isomerization of 25α



solvent	ratio (**25***β*/**25**α)[a]
$(CH_2Cl)_2$	2:1
DME	2:1
CH_3NO_2	6:1
CH_3CN	8.5:1

PPTS in MeOH−CH_2Cl_2 at 0 °C to produce the HI ring alcohol **9** in 94% yield.

Synthesis of the Right Wing of CTX3C. The required fragments now secured, coupling and subsequent construction of the JK ring of CTX3C **1** were pursued (Scheme 5). Condensation of alcohol **9** and carboxylic acid **10** using the Yamaguchi protocol[20] produced the corresponding ester **38** in 90% yield. Construction of the J ring from **38** through C−C bond formation was challenging because of the steric hindrance at C42 and the complexity of the molecule. We previously demonstrated that intramolecular carbonyl olefination using the low-valent titanium reagent developed by Takeda[21] was powerful protocol for cyclization of a similar, less functionalized substrate.[11] Indeed, this reaction was also successful for tetracyclic **38**; treatment of **38** with $Cp_2Ti[P(OEt)_3]_2$ under refluxing THF closed the six-membered J ring to afford **39** in 80% yield.

The next stage of the synthesis involved the stereoselective introduction of hydrogen at C42 and subsequent ketone formation at C41 to prepare for formation of the K ring by reductive etherification (**42***β*, Scheme 5). For this purpose, hydroboration and subsequent alcohol-oxidation of **39** appeared to be the most logical choice. Disappointingly, hydroboration of enol ether **39**, followed by oxidative workup, led predominantly to the wrong stereoisomer **40** (**40**/**41** = 3:1, 76% combined yield). Because the stereoselectivity of this hydroboration was opposite to that expected based on other literature examples,[22] the preferred formation of the undesired product **40** was considered to originate from the intrinsic conformation of **39**. As illustrated in Figure 2, the 1,3-allylic strain in **39** would align H41 and H43 in a syn relationship, and indeed this is supported by the observed ROE. Thus, the sterically demanding LM ring portion projects toward the *β*-face in this conformation, the reagent attacks from the less congested α-face, and **40** is obtained in preference over desired stereoisomer **41**.

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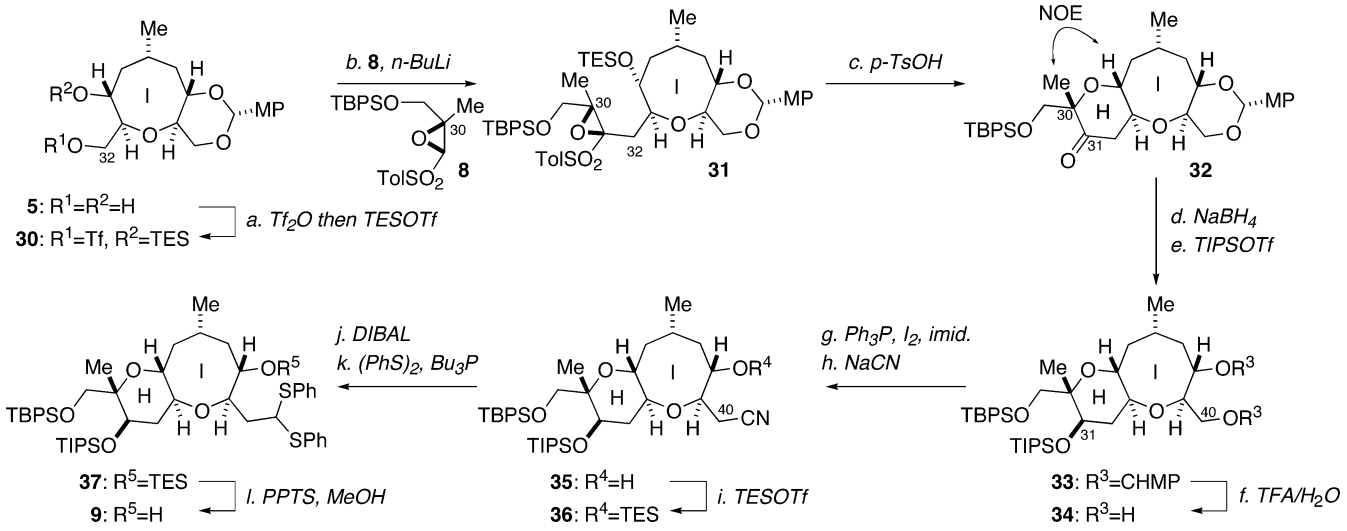
SCHEME 4. Synthesis of the HI Ring[a]



[a] Reagents and conditions: (a) Tf_2O, 2,6-lutidine, 4 Å MS, CH_2Cl_2, then TESOTf, −78 °C; (b) **8**, *n*-BuLi, HMPA, THF, −110 °C; (c) *p*-TsOH·H_2O, $CHCl_3$, $(MeO)_2CH$(*p*-MeOPh), rt to 40 °C, 51% (three steps); (d) $NaBH_4$, CH_2Cl_2/MeOH (1:1), −78 °C, 100%; (e) TIPSOTf, 2,6-lutidine, $(CH_2Cl)_2$, 50 °C, 100%; (f) TFA/THF/H_2O (1:10:5), rt, 87%; (g) Ph_3P, I_2, imidazole, 4 Å MS, THF, −30 °C to 0 °C, 87%; (h) NaCN, DMSO, 40 °C, 99%; (i) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 100%; (j) DIBAL, CH_2Cl_2, −78 °C; (k) PhSSPh, *n*-Bu_3P, 40 °C, 83% (two steps); (l) PPTS, MeOH/CH_2Cl_2 (5:1), 0 °C, 94%.

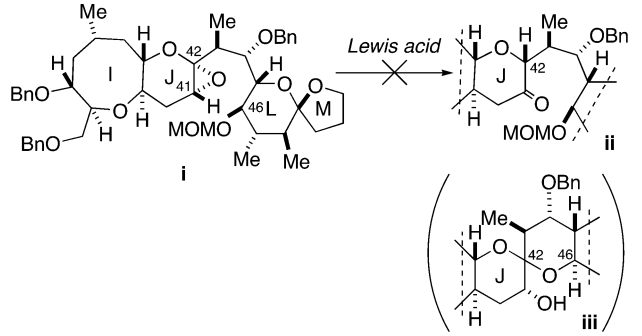
Oxidation of the mixture of **40** and **41** with Dess−Martin periodinane gave a separable mixture of ketones **42**α (71%) and **42**β (24%). The major isomer **42**α could be converted to **42**β by DBU-mediated isomerization, but the ratio obtained of **42**α and **42**β was 1:1. Thus, three cycles of the isomerization-separation sequence were applied to obtain **42**β in 60% yield along with the recovered **42**α in 19% yield.

Although a synthetic route to **42**β was secured, this procedure involved repeated isomerization reactions, and was not sufficiently practical. A more stereoselective route to **42**β was subsequently developed (Scheme 6). Interestingly, epoxidation of **39** using dimethyldioxirane (DMDO)[23] was found to occur selectively to give α-epoxide **43**, again indicating the strong conformational bias of **39** to accept the reagent from the α-face. Having realized the stereoselective oxidation of enol ether **39**, this alternative synthesis aimed to establish the C42 stereocenter through the regio- and stereoselective reduction of **43**.[24] It was presumed that the correct isomer **44** would be formed by S_N2-type hydride delivery to the C42-acetal epoxide of **43**. However, this type of reaction was not predicted to occur easily, because of the presumed low reactivity of the sterically congested C42 as well as the low accessibility of the hydride to the shielded β-face of **43**. Furthermore, it was possible that the activated epoxide would readily form oxonium cation **45**,[25] which could lead to the incorrect isomer **40** via α-hydride attack.

With these considerations in mind, the reagents and conditions were carefully screened (Scheme 6). First, sodium cyanoborohydride was used with a weak activator such as trifluoroethanol or water[26] but the product was only a mixture of isomers **44** and **40** (entry 1 and 2). Whereas sodium borohydride did not react at all with the epoxide (entry 3), lithium borohydride generated the undesired isomer **40** as the sole product (entry 4). The screening was satisfactorily concluded with the extremely potent reductant $LiBHEt_3$,[27] known to generally react in an S_N2 manner (entry 5). Treatment of **43** with $LiBHEt_3$ exclusively led to the desired product **44** in 85% yield (**44**/**40** = 15:1). Alcohol **44** was then oxidized with Dess−Martin periodinane to afford **42**β in 95% yield. Thus, the C42-stereogenic center was successfully installed by means of epoxidation and reduction. Significantly, the stereoselectivity of this method is complementary to that of hydroboration, and thus the protocol developed here

(23) (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187−1201. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205−211. (c) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419.

(24) We also attempted the 1,2-hydride shift of epoxide **i** using various Lewis acids directly to obtain **ii**. However, only 6,6-spiroacetal **iii** was observed as a major product, which arose from the nucleophilic attack of C46-oxygen and concomitant loss of the MOM group. For a successful application of the related 1,2-hydride shift, see: Bazin, H. G.; Wolff, M. W.; Linhardt, R. J. *J. Org. Chem.* **1999**, *64*, 144−152.

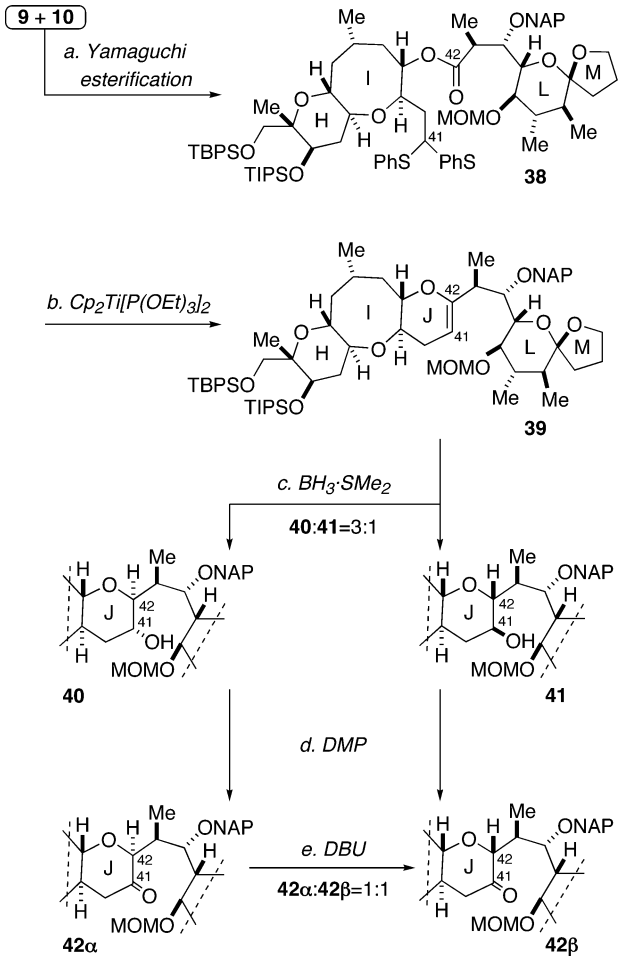


(25) For reduction of the related epoxy acetals presumably through oxocarbenium cation, see: (a) Nicolaou, K. C.; Prasad, C. V. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1990**, *112*, 4988−4989. (b) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616−2617. (c) Cox, J. M.; Rainier, J. D. *Org. Lett.* **2001**, *3*, 2919−2922. (d) Majumder, U.; Cox, J. M.; Rainier, J. D. *Org. Lett.* **2003**, *5*, 913−916. see also 9a, c.

(26) Zimmermann, P. J.; Blanarikova, I.; Jäger, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 910−912.

(27) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486-8487.

SCHEME 5. Synthesis of the J Ring[a]



[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP, 35 °C, 90%; (b) $Cp_2Ti[P(OEt)_3]_2$, THF, reflux, 80%; (c) BH_3·SMe_2, THF, 0 °C to rt, then NaOH, H_2O_2, 76% (**40**/**41** = 3:1); (d) Dess−Martin periodinane (DMP), CH_2Cl_2, **42**α: 71%, **42**β: 24%; (e) DBU, CH_2Cl_2, rt, (**42**α/**42**β = 1:1, after three cycles, **42**α: 19% **42**β: 60%).

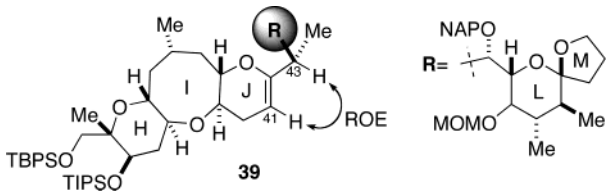
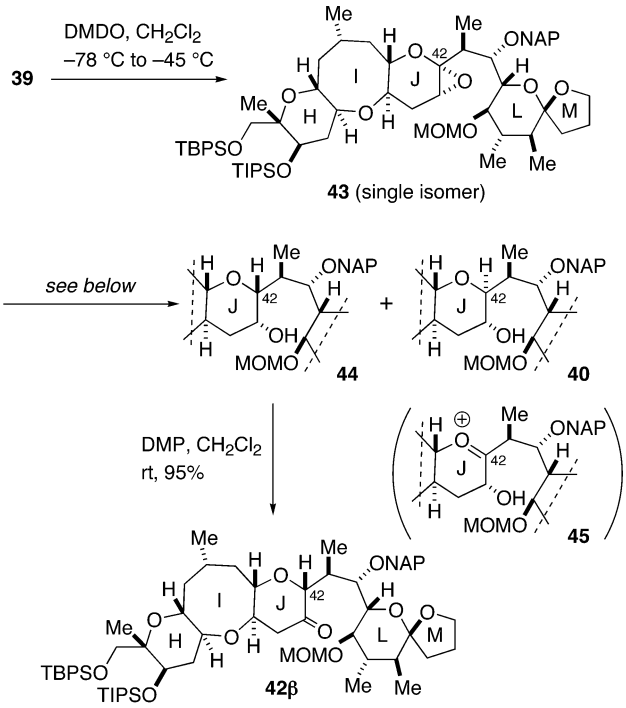


FIGURE 2. Observed ROE and probable local conformation of enol ether **39**.

should be generally applicable to enol ether substrates from which hydroboration leads to undesired selectivity.

Once the correct C42-isomer **42**β was successfully obtained, the remaining tasks for the synthesis of the right wing were formation of the K ring and extension of the carbon chain to the left side (Scheme 7). When **42**β was exposed to triflic acid and $(MeO)_3CH$ in hexane, seven-membered methyl acetal **46** was directly formed with concomitant loss of the MOM group (62% yield). Reductive etherification[28] of acetal **46** using Et_3SiH and BF_3·OEt_2 in the presence of molecular sieves 4A led to construction of the final ether ring to afford the HIJKLM

SCHEME 6. Stereoselective Synthesis of the J Ring



entry	reagents and conditions	**44**:**40**	combined yield
1	$NaBH_3CN$–CF_3CH_2OH, THF, rt	1 : 1.6	90%
2	$NaBH_3CN$–H_2O, THF, rt	1 : 1	84%
3	$NaBH_4$, MeOH, rt	–	no reaction
4	$LiBH_4$, THF, 0 °C	0 : 1	50%
5	$LiBHEt_3$, THF, 0 °C	15 : 1	90%

ring system **47** in 81% yield. The ^1H-^1H coupling constant ($J_{41,42}$ = 9.5 Hz) of **47** verified the axial-attack of the hydride. In this way, the JK ring was assembled from fragment **9** in only 7 synthetic operations.

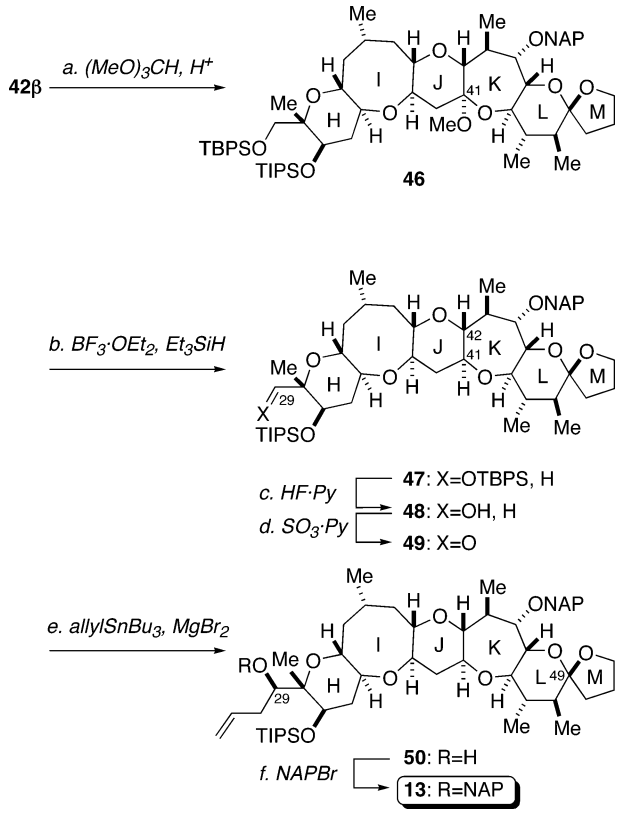
To complete the synthesis of the right wing of CTX3C, the carbon chain corresponding to the G ring was introduced (Scheme 7). HF·pyridine effected the selective removal of the primary TBPS of **47** in the presence of the secondary TIPS to afford **48** (91% yield), which was in turn oxidized with SO_3·pyridine to **49**. Aldehyde **49** was subjected to $MgBr_2$-promoted allylation[29] using allyltributyltin and then the partially formed C49-acetal epimer was re-isomerized using CSA to generate alcohol **50** (73%) and the C29-epimer (12%). Finally, NAP protection of **50** gave rise to the targeted right wing **13** in 98% yield.

Synthesis of the Right Wing of 51-hydroxyCTX3C. As shown in Scheme 8, right wing **14** of 51-hydroxyCTX3C was synthesized from the fragments **9** and **11** similarly to the route described for **13**. The HI ring segment **9** was coupled with the 51-hydroxy LM ring **11** using Yamagu-

(28) (a) Oishi, T.; Nagumo, Y.; Shoji, M.; Le Brazidec, J.-Y.; Uehara, H.; Hirama, M. *Chem. Commun.* **1999**, 2035−2036. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976−4978. (c) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136−4137.

(29) Charette, A. B.; Mellon, C.; Rouillard, L.; Malenfant, É. *Synlett* **1993**, 81−82.

SCHEME 7. Synthesis of the Right Wing of CTX3C[a]



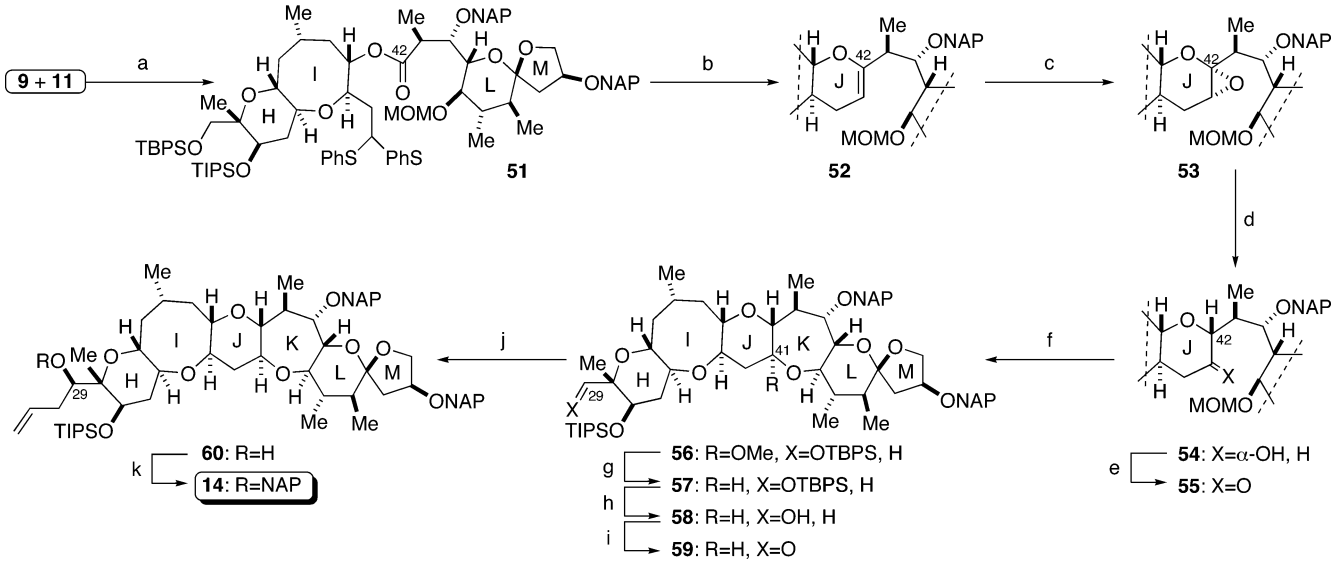
[a] Reagents and conditions: (a) TfOH, $(MeO)_3CH$, hexane, rt, 62%; (b) $BF_3{\cdot}OEt_2$, Et_3SiH, 4 Å MS, CH_2Cl_2, −50 to −20 °C, 81%; (c) HF·Py, Py/THF (1:2), rt, 91%; (d) $SO_3{\cdot}Py$, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C to rt; (e) allylSnBu$_3$, $MgBr_2{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, −78 °C to rt, then CSA, $(CH_2Cl)_2$, rt, 73% (two steps), C29-epimer 12% (two steps); (f) NAPBr, TBAI, NaH, THF/DMF (3:1), rt, 98%.

chi esterification to give **51** in 77% yield. Treatment of **51** with the low-valent titanium complex $Cp_2Ti[P(OEt)_3]_2$ in refluxing THF generated enol ether **52** in 68% yield. DMDO-epoxidation of **52** afforded α-epoxide **53** with complete stereocontrol, which was in turn reduced using $LiBHEt_3$ to produce **54** as the predominant isomer in 78% yield for two steps (stereoselectivity at C42 >20:1). The newly formed secondary alcohol of **54** was oxidized to ketone **55** (80%), which was subjected to direct acetalization to give seven-membered methyl acetal **56** in 62% yield. Lewis-acid promoted reductive etherification of **56** set the C41-stereocenter, leading to hexacyclic ether **57** (78% yield). Selective removal of the TBPS group (76% yield), followed by Swern oxidation, converted **58** to aldehyde **59**, to which allylstannane addition in the presence of $MgBr_2$ installed the C29 stereogenic center to form **60** in 69% yield (two steps). Finally, the C29-secondary alcohol was protected as its NAP ether to afford right wing **14** of 51-hydroxyCTX3C in 91% yield. The coupling and JK ring construction outlined were shown to be applicable to the right wings of ciguatoxins (**1**,**2**,**3**,**4**).

Conclusions

In conclusion, the ciguatoxin right wings (**13** and **14**), which can be readily coupled with the left wings after modification of the terminal olefin, were synthesized in a stereoselective fashion using a significantly improved protocol. The key transformations in the synthesis are an oxiranyl anion strategy to attach the I ring, intramolecular carbonyl olefination to cyclize the J ring and regio- and stereoselective reduction of the epoxyacetal to install the C42-stereocenter. The present procedure greatly improved the efficiency in comparison to previous syntheses. In particular, the utilization of the epoxyacetal approach contributed to a high overall stereoselectivity

SCHEME 8. Synthesis of the Right Wing of 51-HydroxyCTX3C[a]



[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, then DMAP, 35 °C, 77%; (b) $Cp_2Ti[P(OEt)_3]_2$, THF, reflux, 68%; (c) DMDO, CH_2Cl_2, −40 to 0 °C; (d) $LiBHEt_3$, THF, 0 °C to rt, 78% (two steps); (e) Dess−Martin periodinane, CH_2Cl_2, 80%; (f) TfOH, $(MeO)_3CH$, hexane, rt, 62%; (g) $BF_3{\cdot}OEt_2$, Et_3SiH, 4 Å MS, CH_2Cl_2, −50 to −20 °C, 78%; (h) HF·Py, Py/THF (1:2), rt, 76%; (i) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C; (j) allylSnBu$_3$, $MgBr_2{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, −78 °C to rt, 69% (two steps), C29-epimer 14% (two steps); (k) NAPBr, TBAI, NaH, THF/DMF (3:1), rt, 91%.

of the synthesis. Remarkably, only 23 steps were required from monocyclic I ring **5** to the right wings of ciguatoxins, whereas the previous procedure for **11** involved 35 steps.[11] The high practicality of the synthesis established here ensures a supply of these complex fragments for total syntheses and biomedical applications. These studies are now under active investigation in our laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (S) from the Japan Society for the Promotion of Science (JSPS). We are grateful to Dr. Takashi Iwashita and Dr. Tsuyoshi Fujita of Suntory Institute for Bioorganic Research for their high-resolution mass spectroscopy measurements.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H NMR spectra data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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