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Practical Route to the Left Wing of CTX1B and Total Syntheses of CTX1B and 54-deoxyCTX1B

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Abstract: Ciguatoxins, the principal causative agents of ciguatera seafood poisoning, are extremely large polycyclic ethers. We report herein a reliable route for constructing the left wing of CTX1B, which possesses the acid/base/oxidant-sensitive bisallylic ether moiety, by a 6-*exo* radical cyclization/ring-closing metathesis strategy. This new route enabled us to achieve the second-generation total synthesis of CTX1B and the first synthesis of 54-deoxyCTX1B.

Introduction

Ciguatera seafood poisoning, an important medical issue in tropical and subtropical regions, causes gastrointestinal, cardiovascular, and neurological disorders that may last for weeks or even years.[1] It is estimated that more than 50000 people annually are afflicted by this poisoning. Yasumoto and colleagues revealed that ciguatoxins, the causative toxins of ciguatera, are originally produced by an epiphytic dinoflagellata, *Gambierdiscus toxicus*.[2] Since the Yasumoto group elucidated the structures of ciguatoxins in 1989, more than twenty natural ciguatoxins have been described.[3] Ciguatoxins have a ladderlike polycyclic ether structure with five- to nine-membered ring sizes, and exhibit potent toxicities (LD_{50} = 0.25–4 μgkg^{-1}, mice) by binding to the voltage-sensitive sodium channels (VSSC) of excitable membranes.[4,5]

Because of their important bioactivities and intriguing molecular architectures, ciguatoxins have been challenging targets for organic synthesis.[6] In 2001, our group reported the first synthesis of a ciguatoxin congener, CTX3C.[7] Subsequently, we succeeded in the syntheses of two other Pacific ciguatoxins, 51-hydroxyCTX3C and CTX1B (**1**).[8] Our unified strategy realized an efficient assembly of the polyfunctionalized left and right fragments (e.g., **3** + **4a** → **1**, Figure 1).[7,8] Furthermore, we developed a sandwich enzyme-linked immunosorbent assay (ELISA) for their detection.[9] The synthetic ciguatoxins and their fragments[10] have enabled us to investigate the SAR and electrophysical properties of ciguatoxins to understand ciguatoxin–VSSC interactions.[11] However, a more practical route to the left wing (**3**) of CTX1B (**1**)[10c] still needs to be developed.

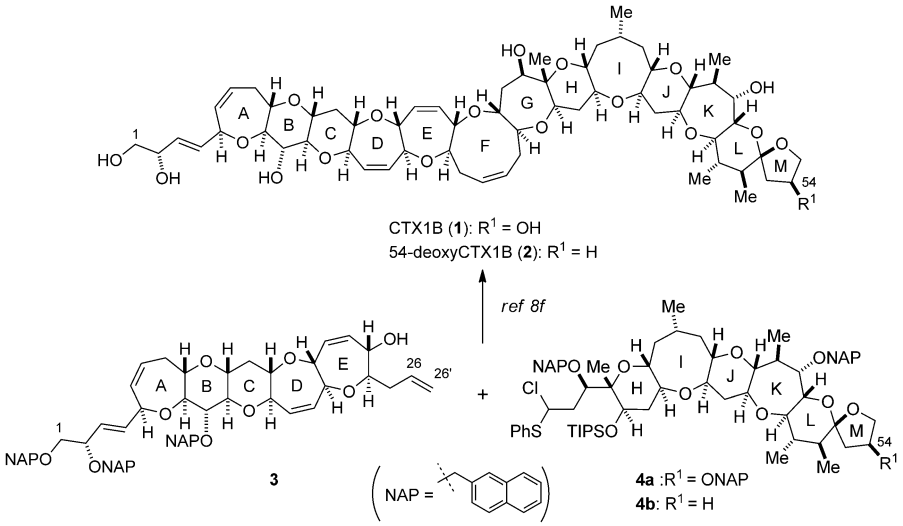

Figure 1. Structures of ciguatoxins.

We have investigated three routes to construct *trans*-fused polyether systems utilizing radical reactions: 1) an acyl radical cyclization/reductive etherification sequence,[10e,12] 2) a 7-*exo* radical cyclization using an electron-deficient acrylate/ring-clos-

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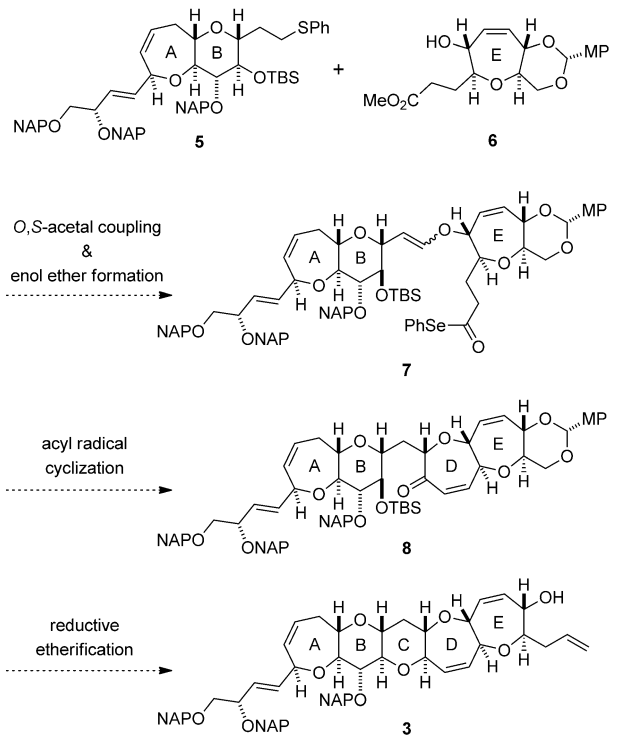
ing olefin metathesis (RCM) sequence,[7,8,13] and 3) a 6-*exo* radical cyclization using a *cis*-vinyl sulfoxide/RCM sequence.[8g,14] In this paper we describe a full account of our reliable and scalable route to the left wing (**3**), and the second-generation synthesis of **1** as well as the first synthesis of 54-deoxyCTX1B (**2**).



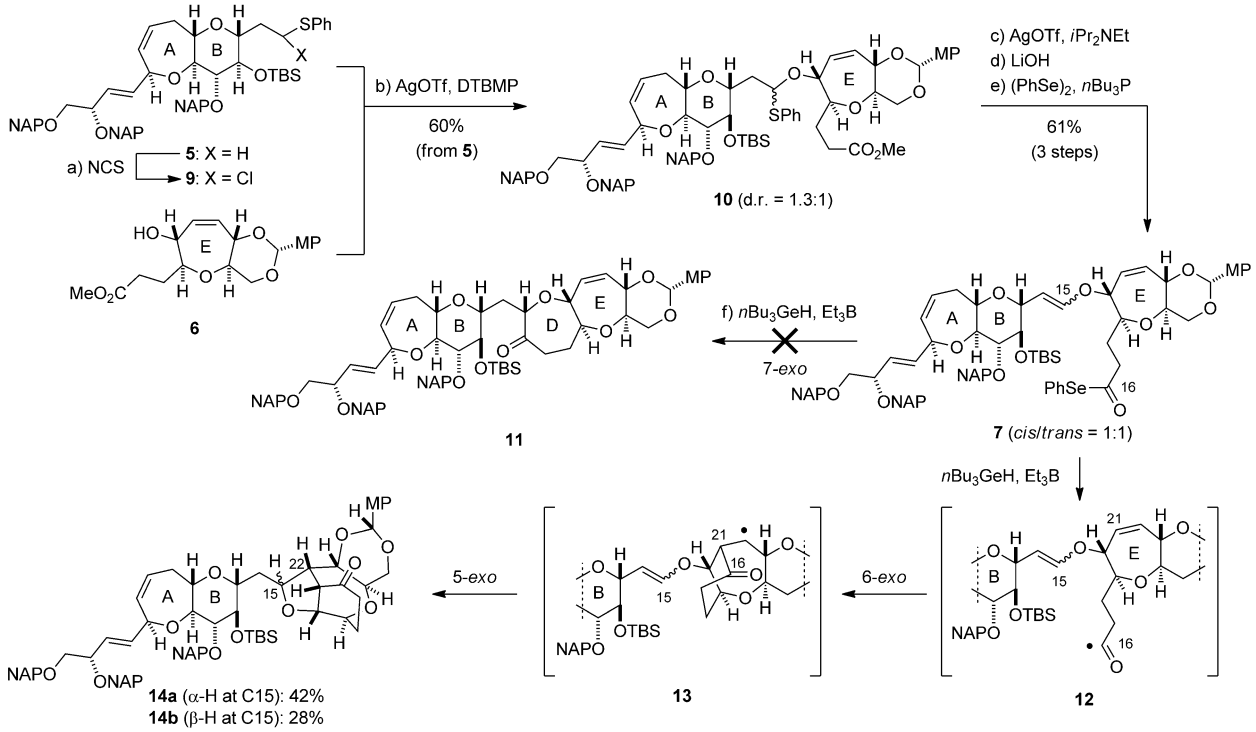
Scheme 1. Initial synthetic plan of left wing (**3**).

Results and Discussion

A new synthetic plan for the left wing (**3**) is shown in Scheme 1. It was envisioned that the *O,S*-acetal-forming coupling between the AB-ring **5** and the E-ring **6**, followed by elimination of PhSH, would afford the enol ether **7**. The seven-membered D-ring could be constructed from **7** through acyl radical cyclization and enone formation. Reductive etherification of enone **8** would culminate in the target left wing **3**.

Synthesis of the acyl radical precursor **7** began with the AB-ring **5**,[15] which possesses the dihydroxybutenyl side chain at the C5 position (Scheme 2). After careful chlorination of sulfide **5** with freshly recrystallized *N*-chlorosuccinimide,[16] the resultant α-chlorosulfide **9** was coupled with the E-ring alcohol **6**[15] through the silver-mediated *O,S*-acetal formation to give **10** (60% from **5**).[17] Treatment of **10** with AgOTf and Hünig's base in benzene, followed by hydrolysis and then seleno esterification with $(PhSe)_2$ and nBu_3P, afforded the enol ether **7** as a 1:1 mixture of *cis*- and *trans*-isomers.[10e,12,18]

In contrast to the successful construction of the CTX3C and C-CTX D-rings,[10e,f] acyl radical cyclization of **7** did not afford the desired seven-membered ketone **11**, despite much effort (Scheme 2). Instead, treatment of **7** with nBu_3GeH[19] and Et_3B at room temperature provided hexacyclic compounds **14a** and **14b**, which were generated through 6-*exo*/5-*exo* tandem radical cyclization (**7**→**12**→**13**→**14**). The high SOMO of the nucle-



Scheme 2. Attempted 7-exo acyl radical cyclization: a) NCS, CCl_4, CH_2Cl_2, RT; b) AgOTf, DTBMP, CH_2Cl_2, 4 Å MS, −78 to −15 °C, 60% (2 steps); c) AgOTf, iPr_2NEt, benzene, 4 Å MS, RT, 87%; d) LiOH·H_2O, 1,4-dioxane, H_2O, RT; e) $(PhSe)_2$, nBu_3P, DMF, RT, 70% (2 steps); f) nBu_3GeH, Et_3B, benzene, RT, **14a**: 42%; **14b**: 28%. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine; NCS = *N*-chlorosuccinimide.

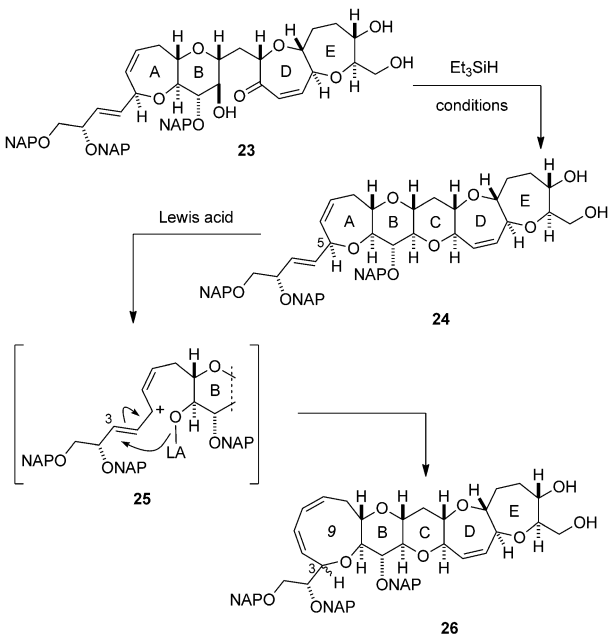
ophilic acyl radical **12** reacted with the low LUMO of the C21–C22 double bond in preference to the high LUMO of the electron-rich enol ether (C14–C15).[20]

Thus, to achieve C–C bond formation between the acyl radical and the C15 position, we turned to the kinetically more favored 6-*exo* cyclization (Scheme 3). The requisite seleno ester **16** was synthesized from **9** and the alcohol **15**,[10 h] which has a one-carbon contracted side chain. Acyl radical cyclization of **16** afforded the desired six-membered ketone **17** with good diastereoselectivity. The yield, however, was low (28%) and the tandem cyclization byproduct **18** was obtained as the major product (34%).

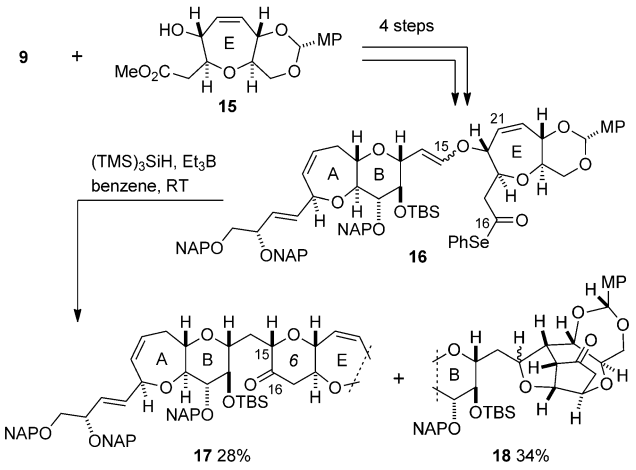
Practical and reliable construction of the D-ring by acyl radical cyclization was then achieved using the C21–C22 saturated E-ring[15] (Scheme 4). Treatment of **20** under the radical conditions afforded the six-membered ether **21** in 64% yield as a single isomer. Ring expansion of ketone **21** according to the Shioiri method ($TMSCHN_2$ and Me_3Al)[21,22] and successive Ito–Saegusa oxidation[23] gave rise to the seven-membered ring **22**. Treatment of **22** with HF·pyridine provided the D-ring enone **23** in 53% overall yield.

The attempted reductive etherification[24] of **23** is summarized in Table 1. Upon treatment of **23** with TMSOTf and $BF_3{\cdot}OEt_2$ in the presence of an excess amount of Et_3SiH in CH_2Cl_2, unexpected nine-membered ether **26** was produced (Table 1, entries 1 and 2). We speculated that formation of **26** entailed the Lewis acid promoted C–O bond cleavage at C5, followed by nine-membered ring formation from bisallylic cation **25**. After many unsuccessful experiments, we found the desired **24** was obtained as a major product by treatment with $BF_3{\cdot}OEt_2$ and Et_3SiH in $MeCN/CH_2Cl_2$ mixed solvents (entry 3). However, a significant amount of **26** was still generated (30–50%). On the basis of these results and the low reproducibility on large-scale synthesis, we were forced to abandon the acyl radical/reductive etherification strategy.

Table 1. Reductive etherification of enone **23**.

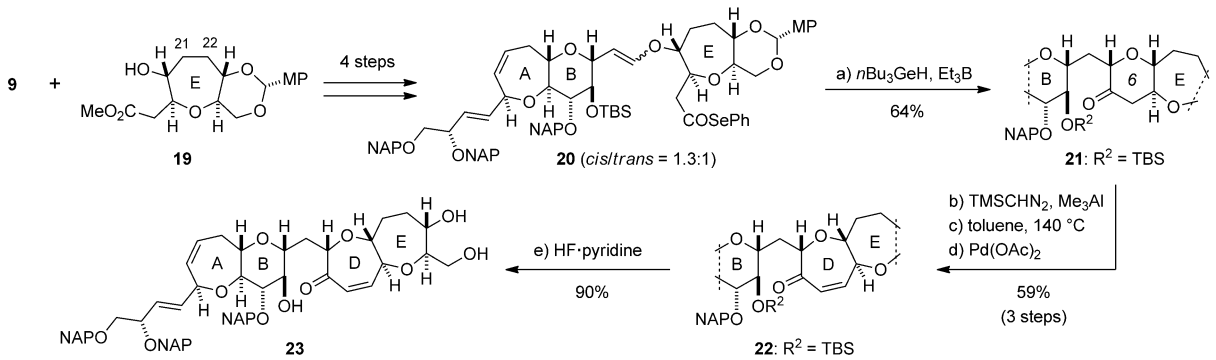


Entry	Conditions	Results
1	TMSOTf, CH_2Cl_2, −78 to −35 °C	**26** 75%
2	$BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to −35 °C	**26** 75%
3	$BF_3{\cdot}OEt_2$, $MeCN/CH_2Cl_2 = 2$, −60 to −10 °C	**24** 30–62%, **26** 50–30%

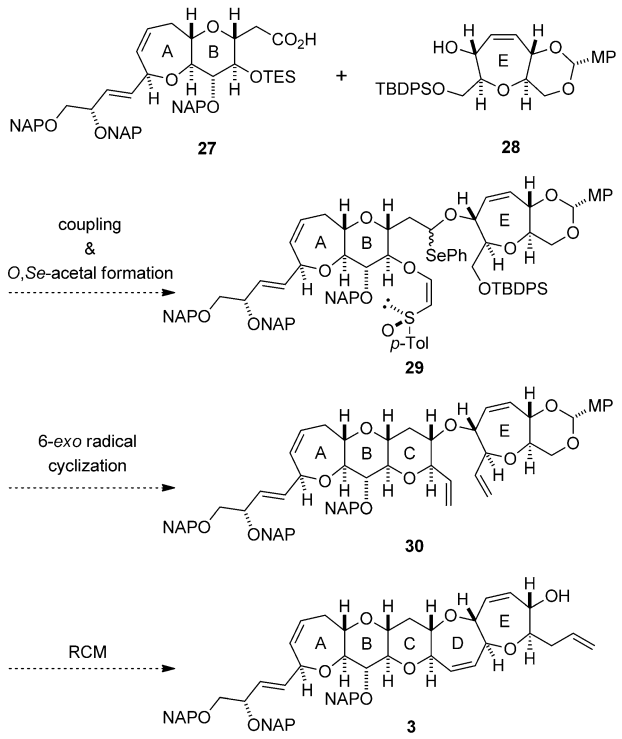


Scheme 3. Attempted acyl radical cyclization of **16** to form six-membered ketone (**17**).

The alternative strategy toward **3** is outlined in Scheme 5. The *O*,*Se*-acetal **29** was chosen as the key intermediate, which



Scheme 4. Synthesis of the D-ring enone **23**: a) nBu_3GeH, Et_3B, benzene, RT, 64%; b) $TMSCHN_2$, Me_3Al, CH_2Cl_2, 4 Å MS, −90 °C; c) toluene, 140 °C; d) $Pd(OAc)_2$, MeCN, RT, 59% (3 steps); e) HF·pyridine, THF, RT, 90%.



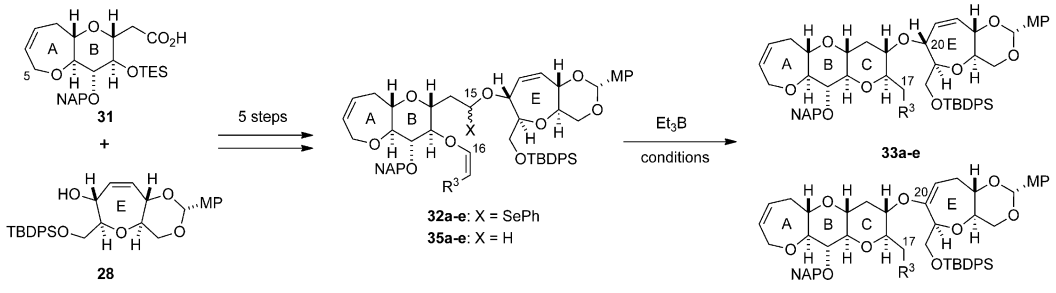
Scheme 5. Alternative strategy toward **3**.

could be prepared from carboxylic acid **27** and alcohol **28**. The synthesis would begin with C-ring formation through 6-*exo* radical cyclization to the *cis*-vinyl sulfoxide **29** as the radical acceptor with a lower LUMO. Next, RCM would afford the seven-membered D-ring. These reaction conditions without the use of strong Lewis acids were expected to establish a practical route to **3** without affecting the bisallylic A-ring system.

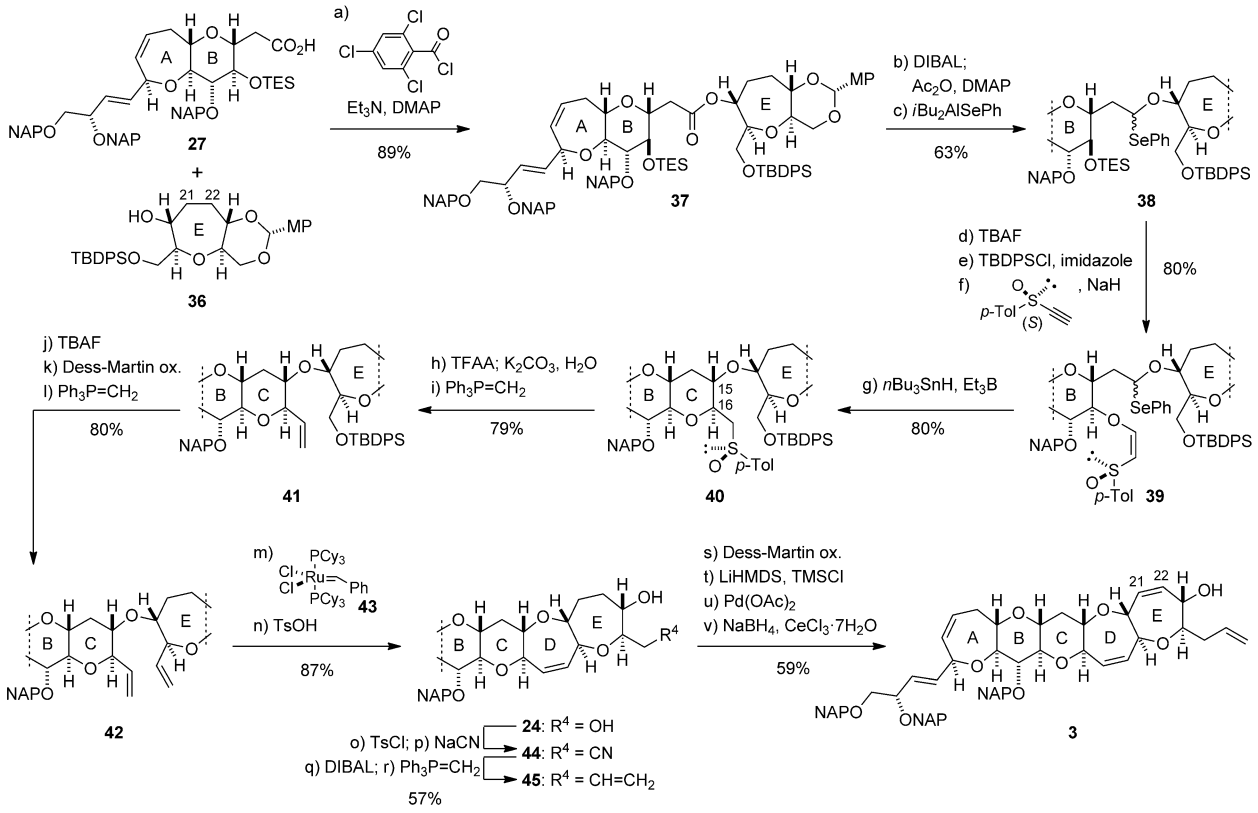
First, the key 6-*exo* radical cyclization was tested in model system **32**[15] (Table 2). The *O*,*Se*-acetal **32** was treated with the conditions optimized for the synthesis of the C-rings of CTX3C and C-CTX (nBu$_3$SnH and Et$_3$B in toluene at −78 °C).[8g,14,25] However, the product was not the desired **33a** but instead enol ether **34a** (Table 2, entry 1). Formation of enol ether **34a** might entail the abstraction of the C20 allylic tertiary hydrogen by the C17 radical, which was generated by C–C bond formation between C15 and C16. Upon treatment with Ph$_3$SnH instead of nBu$_3$SnH, a trace amount of **33a** was formed (entry 2). Although a variety of experimental factors were examined (entries 3–6), **33** was only produced in low yield.

Therefore, we were forced to saturate the C21–C22 double bond of the E-ring to avoid these undesired side reactions. A reliable route to the left wing **3** is described in Scheme 6. Yamaguchi esterification[26] between the AB-ring carboxylic acid **27**[15] and the C21–C22 saturated E-ring alcohol **36**,[15] and subsequent DIBAL reduction and acetylation, gave the *O*,*O*-acetal,[27] which was then converted to the corresponding *O*,*Se*-acetal **38** by the action of iBu$_2$AlSePh[28] in 56% overall yield. Cleavage of the TBDPS- and TES-ethers of **38** with TBAF followed by selective reprotection of the primary alcohol afforded the secondary alcohol, upon which the *cis*-vinyl sulfoxide was installed by the action of NaH and (*S*)-alkynyl sulfoxide[29] to give the radical reaction precursor **39** in 80% overall yield. The 6-*exo* radical cyclization of **39** was conducted with Et$_3$B and nBu$_3$SnH in toluene at −78 °C to furnish the C-ring ether **40** in 80% yield as a single isomer. Pummerer rearrangement[30] of the sulfoxide **40** and Wittig reaction of the resultant aldehyde afforded **41** (79%). TBDPS ether **41** was converted to the olefin **42** through TBAF deprotection, Dess–Martin oxidation,[31] and Wittig olefination in 80% overall yield. Construction of the seven-membered D-ring was achieved using Grubbs' 1st-generation catalyst **43**.[32] Subsequent acid treatment produced

Table 2. Attempted 6-*exo* radical cyclization of **32**.



Entry	R^3		Conditions	Results
1		(*S*) **32a**	nBu$_3$SnH toluene, −78 °C	**33a**: 0%, **34a**: ~50%, **35a**: ~10%
2		(*S*) **32a**	Ph$_3$SnH, benzene, RT	**33a**: trace, **34a**: ~30%, **35a**: ~20%
3		(*R*) **32b**	Ph$_3$SnH, benzene, RT	**33b**: ~10%, **34b**: ~40%, **35b**: ~30%
4		(*S*) **32c**	Ph$_3$SnH, benzene, RT	complex mixture
5		(*R*) **32d**	Ph$_3$SnH, benzene, RT	**33d**: trace, **34d**: ~20%, **35d**: ~40%
6		**32e**	Ph$_3$SnH, benzene, RT	**33e**: trace, **34e**: ~30%, **35e**: ~20%

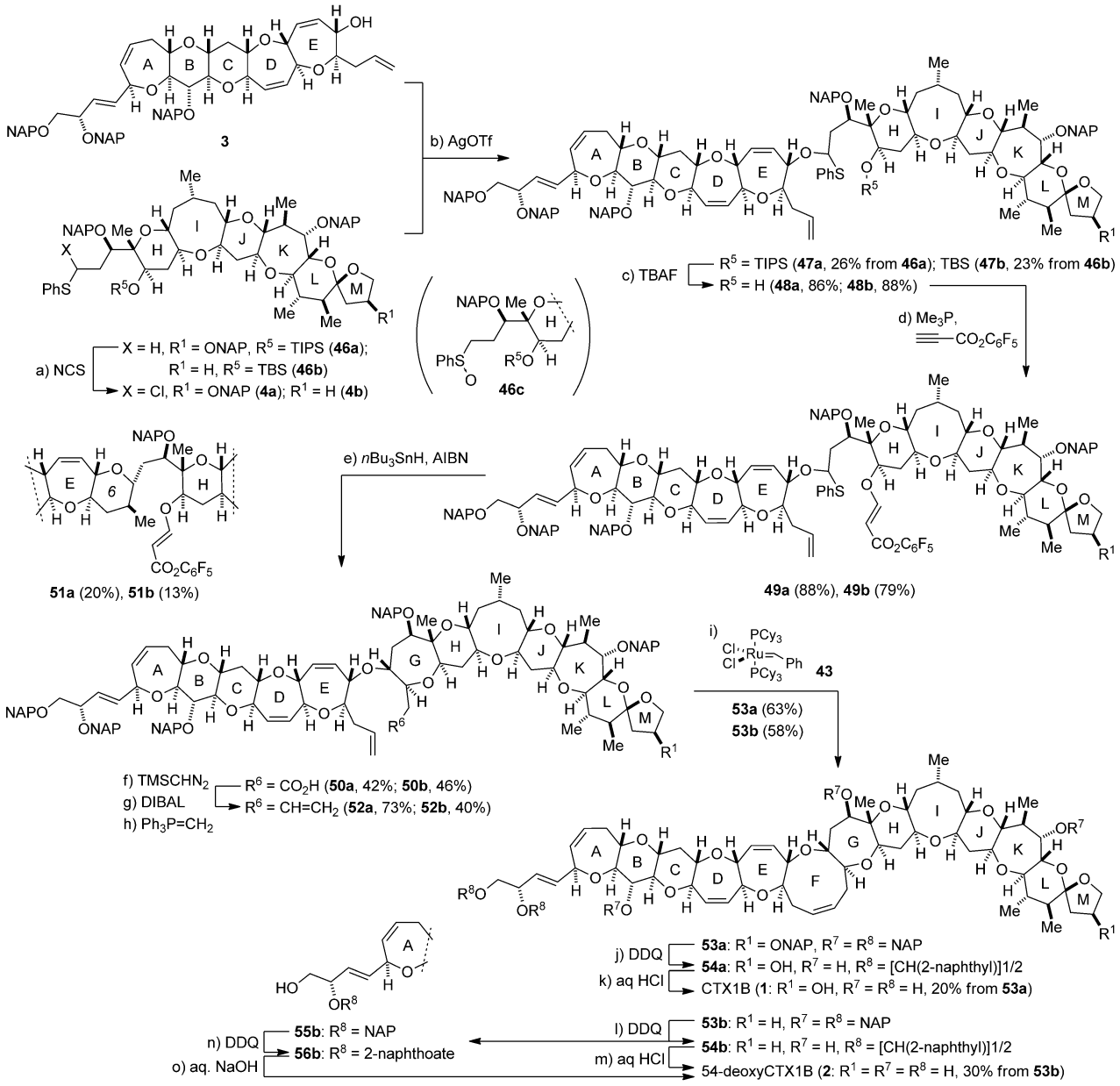


Scheme 6. Practical synthesis of the left wing **3**: a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, RT, 89%; b) DIBAL, CH_2Cl_2, −78 °C; Ac_2O, DMAP, pyridine, −78 to 0 °C, 78%; c) *i*$Bu_2AlSePh$, CH_2Cl_2, hexane, 0 °C, 81%; d) TBAF, THF, RT, 94%; e) TBDPSCl, imidazole, DMF, RT, 94%; f) (*S*)-1-ethynyl *para*-tolyl sulfoxide, NaH, THF, RT, 90%; g) *n*Bu_3SnH, Et_3B, toluene, −78 °C, 80%; h) TFAA, pyridine, MeCN, CH_2Cl_2, 0 °C; K_2CO_3, H_2O, RT to 50 °C; i) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to RT, 79% (2 steps); j) TBAF, THF, RT, 99%; k) Dess–Martin periodinane, CH_2Cl_2, RT, 86%; l) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to RT, 94%; m) **43**, CH_2Cl_2, 40 °C, 89%; n) TsOH·H_2O, CH_2Cl_2, MeOH, RT, 98%; o) TsCl, pyridine, 50 °C; p) NaCN, DMSO, 55 °C, 78% (2 steps); q) DIBAL, CH_2Cl_2, −78 °C; r) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to RT, 73% (2 steps); s) Dess–Martin periodinane, CH_2Cl_2, RT, 92%; t) LiHMDS, TMSCl, Et_3N, THF, −78 °C; u) $Pd(OAc)_2$, MeCN, RT, 70% (2 steps); v) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, CH_2Cl_2, −65 °C, 91%. DIBAL = diisobutylaluminium hydride; DMAP = 4-dimethylaminopyridine; LiHMDS = lithium hexamethyl disilazide; TBAF = tetrabutylammonium fluoride; TFAA = Trifluoroacetic anhydride.

the free diol **44** (87%). Selective tosylation of the primary alcohol of **44** followed by substitution with NaCN furnished the corresponding nitrile, which was transformed to the terminal olefin **45** by DIBAL reduction and Wittig reaction. Finally, the C21–C22 double bond was installed through Dess–Martin oxidation of the C23–OH, Saegusa oxidation, and Luche reduction,[33] giving rise to the left wing (**3**) in 59% overall yield.

With a sufficient amount of the left wing **3** in hand, we launched the most critical coupling reaction, of the left and right wings, **3** and **46**,[34] toward constructing the two major Pacific ciguatoxins, CTX1B (**1**) and 54-deoxyCTX1B (**2**), as described in Scheme 7. Chlorination of the right wing sulfide **46a**[8f,34] was carried out using freshly recrystallized NCS, and the resultant α-chlorosulfide **4a** was coupled without purification to the left wing alcohol **3** (3 equiv) by the action of AgOTf to provide *O*,*S*-acetal **47a**. Despite our efforts, the yield of **47a** was not improved (~26%). An appreciable amount of sulfoxide was always formed, albeit it could be reduced back to **46a** with SO_3-py/NaI. Other chlorinating agents, such as *N*-chlorophthalimide and sulfuryl chloride afforded complex mixtures. Furthermore, alternative methods (e.g., 1) coupling between α-fluorosulfide and alcohol[10k] or 2) esterification of carboxylic acid and alcohol, followed by *O*,*Se*-acetal forming reaction[8g,14]) were unsuccessful. After removal of the TIPS group, the electron-withdrawing pentafluorophenyl acrylate[35] was attached to **48a** to afford **49a** in 75% yield. Formation of the seven-membered G-ring was achieved by radical reaction with *n*Bu_3SnH and AIBN, which gave rise to **50a** in 42% yield along with the 6-*exo* product **51a** (20%).[8f,g] The resulting carboxylic acid **50a** was converted to the corresponding terminal olefin **52a** via methyl ester formation, DIBAL reduction, and Wittig olefination (73%). RCM reaction promoted by Grubbs' catalyst **43** constructed the nine-membered F-ring in 63% yield. Lastly, oxidative removal of the six 2-naphthylmethyl (NAP) groups[36] of **53a** with DDQ (30 equiv, 1.1 μM in CH_2Cl_2/H_2O), followed by acid treatment of the resultant 2-naphthylidene acetal **54a**, furnished **1** in 20% overall yield.

The synthesis of 54-deoxyCTX1B (**2**) was similarly accomplished from **3** and **46b**[8b,34b] except for the final removal of the NAP groups (Scheme 7). Upon treatment of the NAP-protected 54-deoxyCTX1B **53b** with DDQ under slightly diluted conditions (25 equiv, 0.85 μM in CH_2Cl_2/H_2O), a significant amount of mono-NAP ether **55b** was incidentally produced along with naphthoate **56b** and the naphthylidene acetal **54b**.



Scheme 7. Total syntheses of CTX1B (**1**) and 54-deoxyCTX1B (**2**): a) NCS, CCl_4, CH_2Cl_2, RT; b) AgOTf, DTBMP, CH_2Cl_2, CCl_4, 4 Å MS, −78 to 0 °C, **47a**: 26% from **46a**; **47b**: 23% from **46b**; c) TBAF, THF, 35 °C, **48a**: 86%; **48b**: 88%; d) Me_3P, pentafluorophenyl propiolate, CH_2Cl_2, RT, **49a**: 88%; **49b**: 79%; e) nBu_3SnH, AIBN, toluene, 85 °C, **50a**: 42%; **51a**: 20%; **50b**: 46%; **51b**: 13%; f) $TMSCHN_2$, MeOH, benzene, RT; g) DIBAL, CH_2Cl_2, −90 °C; h) Ph_3PCH_3Br, *t*BuOK, THF, 0 °C, **52a**: 73% (3 steps); **52b**: 40% (3 steps); i) **43**, CH_2Cl_2, 40 °C, **53a**: 63%; **53b**: 58%; j) DDQ, CH_2Cl_2, H_2O, RT; k) 1 M HCl, MeOH, RT, **1**: 20% from **53a**; l) DDQ, CH_2Cl_2, H_2O, RT; m) 0.5 M HCl, MeOH, RT; n) DDQ, CH_2Cl_2, RT; o) 5% aq. NaOH, MeOH, RT, **2**: 30% from **53b**. AIBN = azobisisobutyronitrile; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TIPS = triisopropylsilyl.

After several unsuccessful attempts, we found that stepwise procedures afforded **2** from **55b** and **56b**. Thus, DDQ oxidation of **55b** under anhydrous conditions afforded naphthoate **56b**, which was hydrolyzed with aqueous NaOH in MeOH to generate **2**. Acid treatment of the naphthylidene acetal **54b** smoothly gave **2** in 30% combined yield from **53b**.

Conclusion

A practical, reliable, and stereoselective route to the Pacific ciguatoxins, CTX1B (**1**) and 54-deoxyCTX1B (**2**), has been established. Highlights of the total syntheses include: 1) efficient coupling of the AB- and E-rings through Yamaguchi esterification followed by *O,Se*-acetal formation (**27** + **36** → **38**); 2) *cis*-selective installation of vinyl sulfoxide as a radical acceptor (**38** → **39**); 3) stereoselective construction of the C-ring by 6-*exo* radical cyclization (**39** → **40**); 4) seven-membered D-ring formation by RCM reaction (**42** → **44**); 5) *O,S*-acetal formation to connect the polyfunctionalized left and right wings (**3** + **46** → **47**); 6) 7-*exo* radical cyclization to form the G-ring in a stereoselective manner (**49** → **50**); 7) RCM reaction to form the F-ring (**52** → **53**); and 8) global deprotection of NAP-ethers to afford CTX1B

and 54-deoxyCTX1B (**53**→**1** and **2**). It is noteworthy that no significant decomposition of the A-ring bisallylic ether system was observed in any of the steps of the latest successful route. Synthetic fragment **3** and ciguatoxins **1** and **2** will play key roles in the preparation of antibodies for controlling ciguatera seafood poisoning and the analysis of the causative toxins in ciguatera fish poisoning globally,[3d] and furthermore, in understanding the mechanism of action of the symptomatology of ciguatera food poisoning and its long-term neurological symptoms.[4]

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Keywords: ciguatoxin · polycyclic ether · radical reaction · ring-closing metathesis · total synthesis

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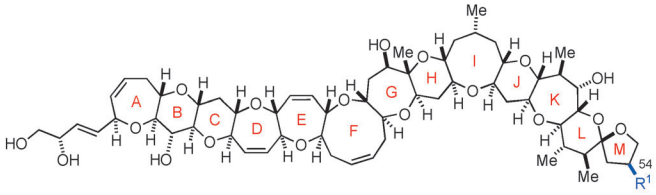

Try, try again! Ciguatoxins, the principal causative agents of ciguatera seafood poisoning, are extremely large polycyclic ethers. A route to the left wing utilizing radical cyclization realized a practical total syntheses of CTX1B and 54-hydroxyCTX1B (see figure).

Organic Chemistry

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Practical Route to the Left Wing of CTX1B and Total Syntheses of CTX1B and 54-deoxyCTX1B