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Convergent synthesis of the ABCDE-ring fragment of the Caribbean ciguatoxin C-CTX-1

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Abstract—Ciguatoxin C-CTX-1 was isolated as a principal causative toxin of ciguatera seafood poisoning in the Caribbean Sea, and is structurally classified as a ladder-shaped polycyclic ether. In this Letter, we report the convergent synthesis of the pentacyclic left half of C-CTX-1, based on a newly developed acyl radical strategy.

Ciguatera poisoning is a human intoxication caused by ingestion of tropical fishes contaminated with ciguatoxins (CTXs).[1] Ciguatera is especially widespread in the islands of the Pacific Ocean, Indian Ocean, and the Caribbean Sea, but cases are increasingly being reported in temperate regions with the expansion of tourism and trade. CTXs arise from precursors that are synthesized by the benthic dinoflagellate *Gambierdiscus toxicus* and are transferred to fishes at different trophic levels within the marine food chain. It is now apparent that chemically distinct CTXs are responsible for ciguatera in different regions. Approximately 20 Pacific CTXs[2] (e.g., CTX3C **1**,[2b] Fig. 1), and two Caribbean ciguatoxins (e.g., C-CTX-1 **2**[3]) have been structurally determined to date.

Current difficulties in predicting, detecting, and treating ciguatera mean that this form of fish poisoning continues to have large socioeconomic impacts, particularly in developing countries. Recently, we raised antibodies against a synthetic fragment of Pacific ciguatoxin CTX3C **1**, and applied them in an enzyme-linked immunosorbent assay (ELISA) format designed to detect **1** specifically.[4] Because of their significant structural differences from Pacific ciguatoxins, development of an alternative detection method for Caribbean ciguatoxins is necessary.

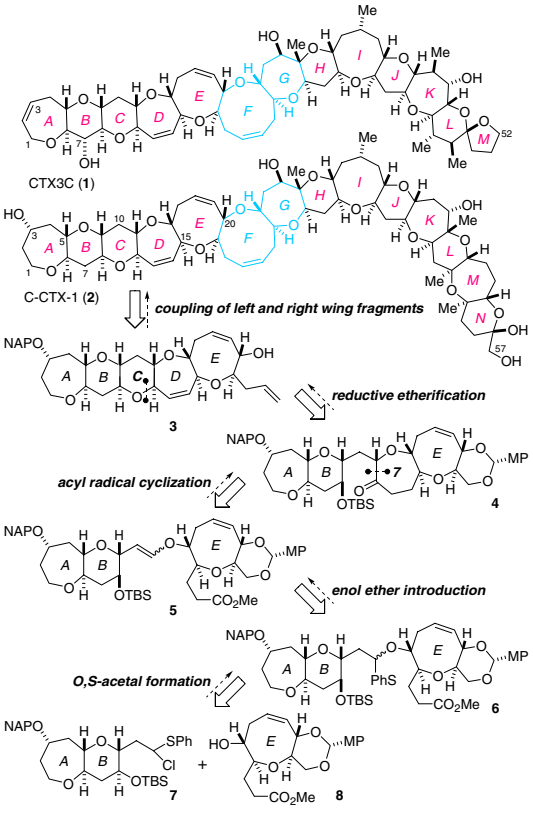

Figure 1. Structures of Caribbean ciguatoxin C-CTX-1 and Pacific ciguatoxin CTX3C, and retrosynthesis of the left wing fragment of C-CTX-1.

Keywords: Ciguatoxins; Polyethers; Radicals; Enol ethers; O,S-Acetals.
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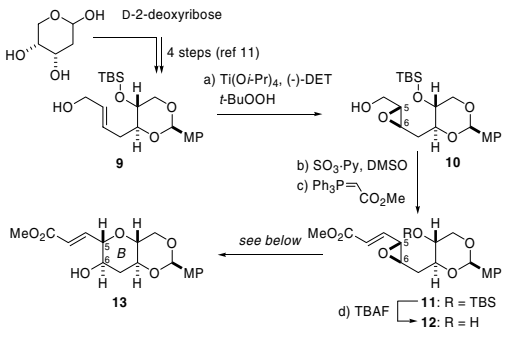
In this context, we launched a program directed toward the total synthesis of C-CTX-1 **2** (Fig. 1).[5] The synthetic plan for **2** was based on our previous total syntheses of Pacific ciguatoxins such as **1**: coupling between the ABCDE- and HIJKLM-ring fragments with subsequent construction of the central FG-ring system (blue highlighting in Fig. 1) generated the entire structure of **1**.[6] Since **1** and **2** share the common FG-ring structures, we planned to utilize this unified convergent strategy for construction of **2**. The dissected left half **3** was further retrosynthetically disconnected to afford simple bicyclic **7** and monocyclic **8**. In the synthetic direction, we envisaged assembling these AB- and E-ring systems into **3** using the recently developed acyl radical methodology that we previously applied to the concise synthesis of the ABCDE-ring fragment of **1**.[7] Namely, after linking **7** and **8** by forming the C–O bond as its O,S-acetal **6**,[8] elimination of the sulfide from **6** would produce enol ether **5**, the subsequent acyl radical addition would then cyclize the seven-membered ether ring corresponding to the D-ring (**5**→**4**).[9] The remaining six-membered C-ring of **3** was in turn to be constructed through reductive etherification.[10]

The six-membered B-ring was cyclized via 6-*endo* selective opening of an hydroxy epoxide (Scheme 1). The known allylic alcohol **9**,[11] which was prepared from D-2-deoxyribose in four steps, was subjected to Sharpless asymmetric epoxidation,[12] selectively producing β-epoxide **10**. Following the method developed by Nicolaou,[13] the π-bond was attached to the epoxide unit as a directing unit to induce the kinetically unfavorable 6-*endo* mode cyclization at C5 rather than the 5-*exo* counterpart at C6. Specifically, oxidation of primary alcohol **10**, followed by Wittig olefination, led to α,β-unsaturated ester **11**, the TBS-group of which was removed using TBAF to generate hydroxy epoxide **12**.

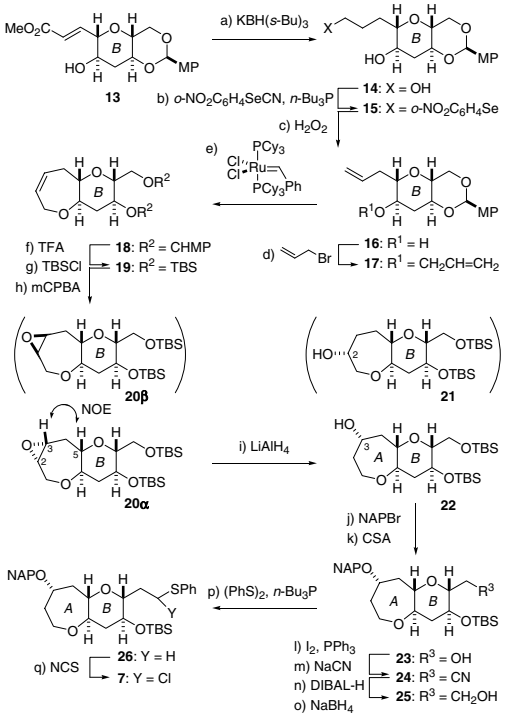
As expected, the acid-catalyst, PPTS, effected selective cleavage of the C–O bond adjacent to the π-bond, leading to the 6-*endo* product **13** in a 41% yield (entry 1, Scheme 1). Since the low yield arose from the acid-induced concomitant removal of the *p*-methoxyphenyl (MP) acetal, the substrate was alternatively treated with PPTS in the presence of $MPCH(OMe)_2$. The yield was increased to 57% as a result, but further optimization was necessary. After screening different reagents and conditions, it was found that $[Rh(CO)_2Cl]_2$-promoted intramolecular ring opening of vinyl epoxides, as reported by Ha,[14] worked well under mild conditions and gave the cyclized product **13** in an 84% yield.[15]



entry	reagents	solvent	temperature (C°)	yield (%)
1	PPTS	CH_2Cl_2	32	41
2	PPTS, $MPCH(OMe)_2$	toluene	80	57
3	$[Rh(CO)_2Cl]_2$	THF	25	84

Scheme 1. Reagents and conditions: (a) Ti(O*i*-Pr)$_4$, (−)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −30 °C, 89%; (b) SO_3·Py, DMSO, Et_3N, CH_2Cl_2, 0 °C; (c) $Ph_3P{=}CHCO_2Me$, THF, rt, 78% (two steps); (d) TBAF, THF, rt, 95%.

The directing group of **13** for the 6-*endo* cyclization was then reduced to a saturated alcohol **14** using KBH(*s*-Bu)$_3$ (Scheme 2).[16] After conversion of **14** to selenide **15** with *o*-nitrophenyl selenocyanate and tributylphosphine,[17] treatment of **15** with hydrogen peroxide gave the selenoxide, which underwent β-elimination to furnish terminal olefin **16**. Introduction of the allyl group onto the secondary alcohol of **16**, and subsequent ring closing olefin metathesis[18] of **17** constructed the seven-membered ether ring of **18**.[19] The MP group of **18** was removed, and the hydroxyl groups of the resultant diol were protected as TBS ethers, producing **19**. Epoxidation of **19** with *m*-CPBA selectively occurred at the



Scheme 2. Reagents and conditions: (a) KBH(*s*-Bu)$_3$, THF/EtOH = 100, −78 °C, 80%; (b) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF, rt; (c) H_2O_2, THF, 0 °C to rt; (d) allyl bromide, DMF/THF = 1/5, 0 °C, 70% (three steps); (e) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, rt, 96%; (f) TFA, THF/H_2O = 3.6, rt; (g) TBSCl, imidazole, DMF, rt, 98% (two steps); (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 99% (**20α**:**20β** = 4.7:1); (i) $LiAlH_4$, Et_2O, −20 °C, 91% (**22**:**21** = 4.1:1); (j) NAPBr, TBAI, NaH, THF/DMF = 3, rt; (k) CSA, MeOH/THF = 1, 0 °C, 51% (two steps); (l) I_2, PPh_3, imidazole, THF, rt, 95%; (m) NaCN, DMSO, 45 °C, 90%; (n) DIBAL-H, CH_2Cl_2, −95 °C, then 1 N HCl aq, rt; (o) $NaBH_4$, MeOH/CH_2Cl_2 = 1, −20 °C to rt, 83%; (p) $(PhS)_2$, *n*-Bu_3P, pyridine, rt, 95%; (q) NCS, CH_2Cl_2/CCl_4 = 1/5, rt.

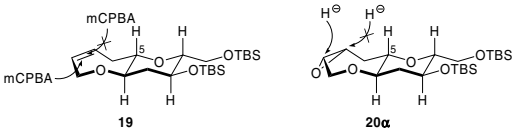


Figure 2. Energy-minimized three-dimensional structures of **19** and **20α** (MM2*, MacroModel Ver. 8.5).

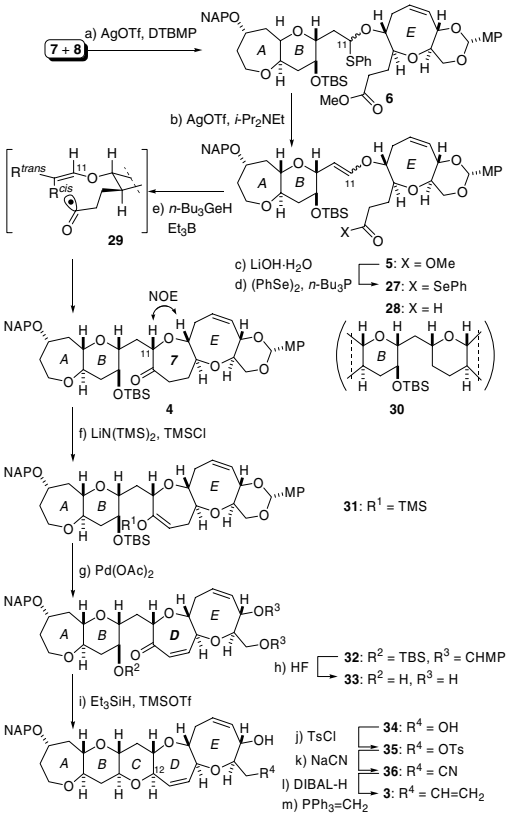
α-face of the molecule, and **20α** was isolated in a 75% yield (**20α**:**20β** = 4.7:1). Reductive opening of epoxide **20α** was promoted by $LiAlH_4$ to generate the desired product **22** as the major isomer (**22**:**21** = 4.1:1).[20] Thus, all the stereocenters necessary for the AB-ring fragment had been successfully introduced by this stage.

As shown in Figure 2, the desirable selectivities observed in the epoxidation and the subsequent reduction were considered to originate from the intrinsic conformations of **19** and **20α**. In both cases, the reagent access route leading to the undesired isomers was sterically blocked by the projecting C5-hydrogen.

An additional eight-step reaction sequence transformed **22** into the coupling substrate **7** (Scheme 2). The secondary alcohol of **22** was converted to its 2-naphthylmethyl (NAP) ether,[21] and the TBS-group at the less-hindered position was selectively removed under acidic conditions, leading to alcohol **23**. A reagent combination of I_2, PPh_3, and imidazole[22] chemoselectively transformed the alcohol of **23** into the iodide, and subsequent cyanide introduction gave the one-carbon homologated product **24**. Then, stepwise reduction of nitrile **24** using DIBAL-H and $NaBH_4$ resulted in alcohol **25**. Finally, treatment of **25** with $(PhS)_2$ and *n*-Bu_3P[23] generated phenylsulfide **26**, and the chloride was subsequently introduced into the α-position of the sulfide by the action of NCS to afford α-chlorosulfide **7**.[24]

As shown in Scheme 3, coupling between the AB-ring electrophile **7** and the E-ring nucleophile **8**[25] was promoted by AgOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to generate adduct **6** as a diastereomeric mixture (dr = 1:1) in a 70% yield.[6,8,26] Efficient C–O bond formation from the hindered secondary alcohol **8** as well as compatibility of the acid sensitive MP acetal proved the high generality of this O,S-acetal formation. The sulfide of adduct **6** was then activated with the same silver salt in the presence of Hünig's base, resulting in effective formation of the chemically labile enol ether **5** as a mixture of geometric isomers (93% yield, cis:trans = 1:2.1).[7,27] Next, the methyl ester of **5** was transformed into phenylselenyl ester **27** via saponification and subsequent treatment with $(PhSe)_2$ and *n*-Bu_3P.[28]

Phenylselenide **27** was then subjected to the radical cyclization conditions (*n*-Bu_3GeH and Et_3B),[29] recently optimized for the synthesis of the ABCDE ring fragment of CTX3C **1**.[7b,30] During this step, acyl radical intermediate **29**, generated through homolytic cleavage of the C–Se bond of **27**, reacted with the enol ether to produce the seven-membered ring in oxepane **4** in a 63% yield



Scheme 3. Reagents and conditions: (a) **8** (1.5 equiv), AgOTf, DTBMP, 4 Å MS, CH_2Cl_2/CCl_4 = 5, −90 °C to −15 °C, 70% from **7** (dr = 1:1); (b) AgOTf, *i*-Pr_2NEt, 4 Å MS, benzene, rt, 93% (cis:trans = 1:2.1); (c) $LiOH{\cdot}H_2O$, 1,4-dioxane/H_2O = 1.7, rt; (d) $(PhSe)_2$, *n*-Bu_3P, DMF, rt, 80% (two steps); (e) *n*-Bu_3GeH, Et_3B, benzene, 63% (**4**), 7% (**28**), 21% (**30**); (f) $LiN(TMS)_2$, TMSCl, THF, −95 °C, 52%; (g) $Pd(OAc)_2$, CH_3CN, rt, 83%; (h) HF aq, CH_3CN, rt; (i) Et_3SiH, TMSOTf, 4 Å MS, CH_2Cl_2, −90 to −15 °C, 86% (two steps); (j) TsCl, pyridine, rt, 75%; (k) NaCN, DMSO, 45 °C, 100%; (l) DIBAL-H, CH_2Cl_2, −90 to −72 °C, then 1 N HCl aq, rt; (m) CH_3PPh_3Br, *t*-BuOK, THF, 0 °C, 37% (two steps).

with complete stereochemical control. This excellent stereocontrol is ascribed to the strongly favored transition state conformation of **29**, in which the $A^{1,3}$-strain is minimized. Although premature reduction and decarbonylation of the acyl radical generated aldehyde **28** (7%) and tetrahydropyran **30** (21%), respectively, as minor byproducts, chemo- and stereoselective intramolecular addition to the electron-rich alkene to form the seven-membered ring as the major product highlights the versatility of the present acyl radical strategy.

Introduction of olefin to oxepane **4** was realized in two steps: regioselective TMS-enol ether formation using a reagent combination of $LiN(TMS)_2$ and TMSCl, followed by Saegusa oxidation[31] of **31** with Pd^{2+} to yield α,β-unsaturated ketone **32**. The TBS and acetal protective groups of **32** were removed with aqueous hydrogen fluoride, resulting in triol **33**. Then, reductive etherification[32] of hydroxy ketone **33**, using TMSOTf and Et_3SiH, established the C12 stereocenter via axial-attack of the hydride on the oxonium cation intermediate, yielding the requisite pentacyclic ABCDE-ring structure **34**. Lastly, the R^4 side chain was modified through standard

functional group manipulations. The primary alcohol of **34** was tosylated to give **35**, which was treated with sodium cyanide to afford **36**. DIBAL-H reduction of nitrile **36** to the aldehyde and subsequent Wittig methylenation delivered the targeted left wing fragment **3**.[33]

In summary, we have synthesized the ABCDE ring fragment **3** of the Caribbean ciguatoxin C-CTX-1 in a highly convergent manner (13 steps from the fragments **7** and **8**). Key reactions of the synthesis include: (i) $[Rh(CO)_2Cl]_2$-catalyzed, 6-*endo* selective, hydroxy epoxide cyclization to construct the B-ring; (ii) stereo- and regioselective introduction of the hydroxy group of the A-ring; (iii) direct construction of the O,S-acetal to couple the AB- and E-ring fragments, and following efficient formation of an electron-rich enol ether; (iv) stereoselective acyl radical cyclization to the seven-membered D-ring; and (v) stereoselective reductive etherification to build the six-membered C-ring. The left wing fragment prepared here will serve both as a hapten for preparing anti-ciguatoxin antibodies to control Caribbean ciguatera and as a fragment for a total synthesis of C-CTX-1.

Acknowledgments

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33. Physical data for **3**: Colorless solid; $[\alpha]_D^{25}$ −81.5 (*c* 0.67, CH_2Cl_2); IR (film) *v* 2928, 2872, 1455, 1353, 1271, 1091, 856, 817, 771 cm^{-1}; ^1H NMR (500 MHz, C_6D_6); δ 7.69 (1H, m, NAP), 7.67–7.63 (3H, m, NAP), 7.41 (1H, dd, $J = 9$, 1.5 Hz, NAP), 7.26 (2H, dddd, $J = 14.5$, 7, 7, 1.5 Hz, NAP), 5.99 (1H, ddt, $J = 17$, 10, 7 Hz, H23), 5.95 (1H, dt, $J = 12.5$, 2.5 Hz, H13), 5.81 (1H, dt, $J = 12.5$, 2.5 Hz, H14), 5.77 (1H, dddd, $J = 11.5$, 11.5, 6.5, 5 Hz, H18), 5.55 (1H, dd, $J = 11.5$, 5 Hz, H19), 5.12 (1H, dd, $J = 17$, 2 Hz, H24′), 5.08 (1H, dt, $J = 10$, 2 Hz, H24′), 4.47 (1H, d, $J = 12$ Hz, NAP), 4.41 (1H, d, $J = 12$ Hz, NAP), 4.14 (1H, dd, $J = 8.5$, 2.5 Hz, H15), 3.99 (1H, m, H20), 3.83–3.78 (2H, m, H1, H12), 3.70 (1H, ddd, $J = 9.5$, 9.5, 3 Hz, H5), 3.55–3.48 (2H, m, H3, H16), 3.18–3.04 (4H, m, H1, H6, H11, H21), 2.92 (1H, ddd, $J = 9$, 7, 4 Hz, H8), 2.87 (1H, ddd, $J = 11$, 8.5, 4 Hz, H9), 2.69–2.59 (2H, m, H17, H22), 2.52–2.47 (2H, m, H4, H7), 2.34 (1H, dt, $J = 8.5$, 4 Hz, H10), 2.22–2.14 (2H, m, H17, H22), 1.91–1.84 (1H, m, H2), 1.82–1.71 (4H, m, H2, H4, H7, 10H); ^{13}C NMR (125 MHz, C_6D_6) δ 137.5, 136.9, 136.0, 135.8, 133.9, 133.5, 131.3, 126.6, 126.4, 126.0, 117.1, 86.1, 84.9, 81.29, 81.25, 79.5, 78.8, 77.8, 76.7, 76.3, 73.0, 72.1, 70.50, 70.45, 66.3, 39.0, 37.8, 37.7, 37.5, 36.8, 32.9, 30.2; HRMS (ESI), calcd for $C_{35}H_{42}O_7Na$ 597.2823 ($M+Na^+$), found 597.2821.