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Studies toward the Total Synthesis of Caribbean Ciguatoxin C-CTX-1: Synthesis of the LMN-Ring Fragment through Reductive Olefin Cross-Coupling

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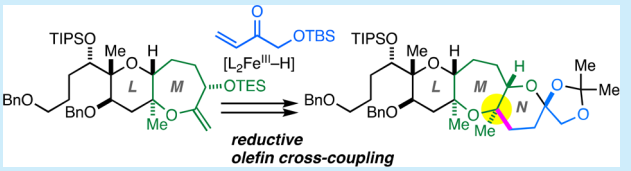
Supporting Information

ABSTRACT: Synthesis of the LMN-ring fragment of Caribbean ciguatoxin C-CTX-1, the principal causative toxin for ciguatera fish poisoning around the Caribbean Sea areas, is described. The key feature of the synthesis is the stereoselective introduction of an angular methyl group on the sterically encumbered seven-membered M-ring by the application of a hydrogen atom transfer-based reductive olefin coupling.



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Ciguatera is a naturally occurring seafood poisoning prevalent in tropical and subtropical regions of the Pacific Ocean, Indian Ocean, and Caribbean Sea with more than 20000−60000 victims annually and continues to be a serious worldwide public health concern.[1,2] Its incidence rates have recently been increasing in temperate regions,[3] and thus, eradication of ciguatera is an urgent global issue that needs to be addressed. Pacific ciguatoxins, the principal causative toxins for ciguatera seafood poisoning in the Pacific Ocean, are produced by the benthic dinoflagellate *Gambierdiscus toxicus* and accumulate in many fish through the food chain; thus, humans are prone to intoxication.[4] To date, more than 20 Pacific ciguatoxin congeners have been isolated and structurally identified.[5]

Caribbean ciguatoxins, the causative toxins for ciguatera around the Caribbean Sea areas, were isolated in 1998 by Lewis and co-workers from the carnivorous fish horse-eye jack (*Caranx latus*).[6] The gross structures, including the relative configurations, of Caribbean ciguatoxin C-CTX-1 (**1**) and a minor analogue C-CTX-2 (**2**) were assigned through extensive 2D NMR studies (Figure 1).[6] The most striking difference in the chemical structure of **1** compared with representative Pacific ciguatoxins, such as CTX3C (**3**),[7] is the right-hand LMN-ring domain. In particular, the presence of the M-ring, a sterically encumbered seven-membered ether ring with two pseudoaxially oriented angular methyl groups flanking the ether oxygen, poses a formidable synthetic challenge.[8] With respect to synthetic strategies toward the M-ring of Caribbean ciguatoxin C-CTX-1, Hirama and co-workers reported two approaches.[9] One included the use of SmI_2-mediated reductive cyclization,[10] and the other utilized [2 + 2] photocycloaddition followed by oxidative cleavage of the resultant cyclobutene structure and enzymatic desymmetrization to construct the sterically congested seven-membered M-ring. We previously reported the synthesis of a similar seven-membered ether substructure seen within gymnocin B,[11] which relied on ring-closing metathesis.[12] However, these prior synthetic approaches lacked the stereoselectivity and efficiency required for practical synthesis. To address these synthetic problems, we decided to develop a new synthetic strategy, and herein we report a synthetic route to the LMN-ring fragment of Caribbean ciguatoxin C-CTX-1 through reductive olefin cross-coupling.

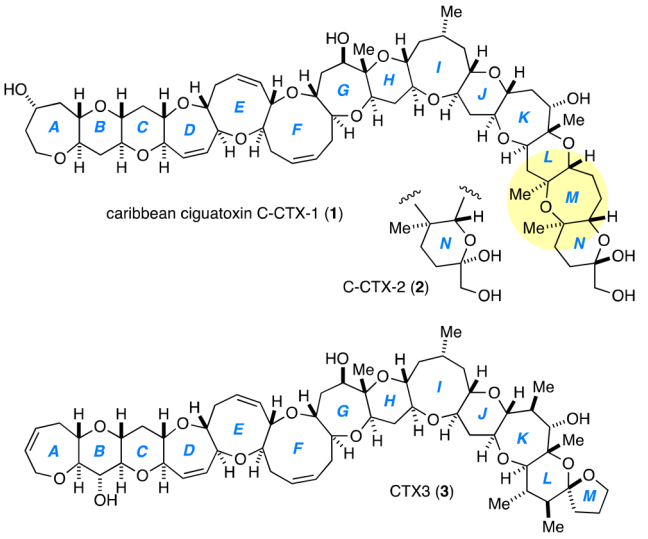

Figure 1. Structures of Caribbeaan ciguatoxins C-CTX-1 (**1**), C-CTX-2 (**2**), and Pacific ciguatoxin CTX3C (**3**).

Our retrosynthetic analysis of the LMN-ring fragment **4** is depicted in Scheme 1. Compound **4** could be accessed from ketone **5** through deprotection and simultaneous hemiacetal formation. To install the four-carbon unit in conjunction with construction of a tetrasubstituted stereogenic center at the highly congested position on the right side of the seven-

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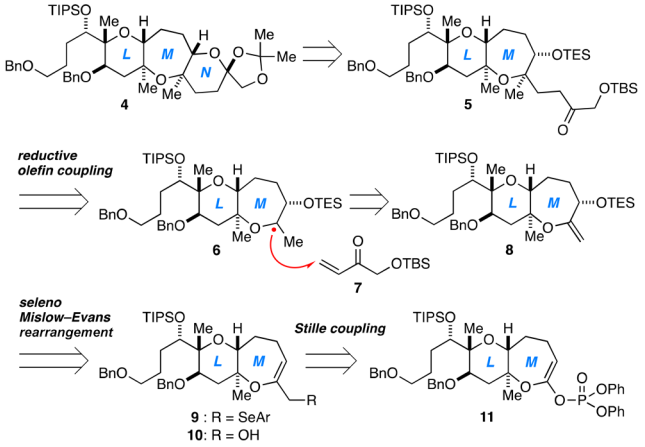
Org. Lett. XXXX, XXX, XXX−XXX

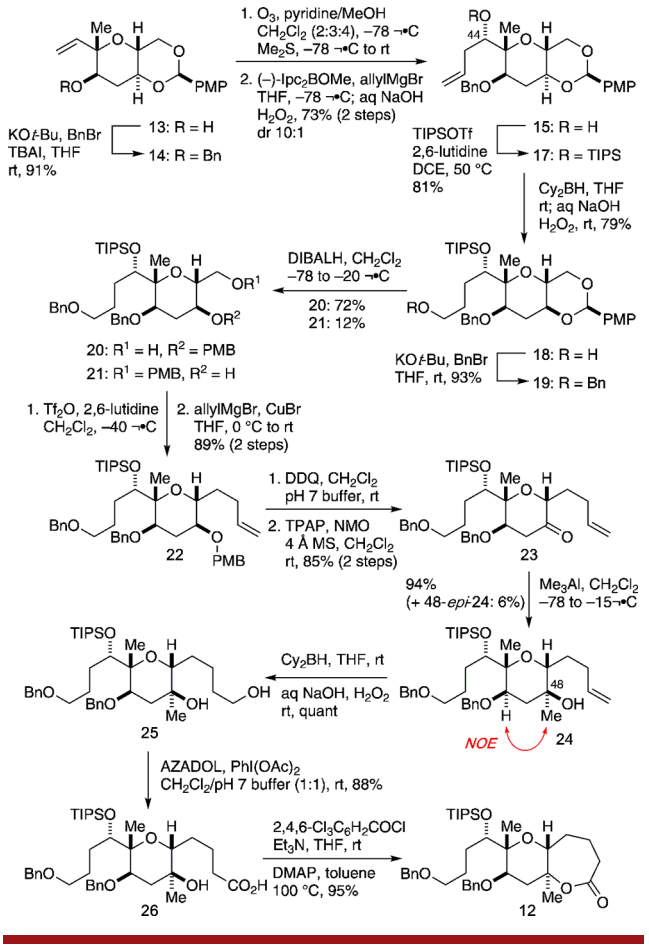
Scheme 1. Retrosynthetic Analysis of LMN-Ring Fragment 4 of C-CTX-1



membered M-ring, we planned to use an intermolecular radical coupling reaction, which is an attractive approach in terms of both reactivity and control of the stereoselectivity.[13] With respect to the generation of carbon radical **6** and subsequent conjugate addition to vinyl ketone **7**,[14] the hydrogen atom transfer (HAT)-based reductive olefin coupling reaction developed by the Baran group[15,16] was envisioned to be the most appealing approach.[17] The precursor *exo*-enol ether **8** would be accessed from allylic selenide **9** by a seleno-Mislow–Evans rearrangement.[18] Selenide **9** would be easily synthesized from allylic alcohol **10**, which in turn would be derived from enol phosphate **11** by Stille coupling with (tributylstannyl)-methanol.[19,20]

The synthesis of seven-membered lactone **12**, the precursor of enol phosphate **11**, started with the known alcohol **13**,[9a] which was protected as the benzyl ether **14** in 91% yield (Scheme 2). Ozonolysis of the terminal olefin within **14** provided the corresponding aldehyde, which was subjected to Brown asymmetric allylboration[21] using (−)-*B*-allyldiisopinocamphenylborane to give homoallylic alcohol **15** in 73% yield for the two steps with a diastereomeric ratio of 10:1. The configuration of the newly generated stereogenic center at C44 was unambiguously established from NOE data after derivatization to obtain bis(acetonide) **16** (Figure 2). After protection of alcohol **15** as its TIPS ether (TIPSOTf, 2,6-lutidine, DCE, 50 °C, 81%), hydroboration of the resulting compound **17** using dicyclohexylborane gave alcohol **18** in 79% yield. At this stage, the C44 diastereomer, which was produced in the Brown allylboration, could be removed by careful flash column chromatography on silica gel. Protection of alcohol **18** as its benzyl ether provided compound **19** in 93% yield. Regioselective reductive cleavage[22] of the *p*-methoxybenzylidene acetal of **19** with DIBALH (CH_2Cl_2, −78 to −20 °C) produced primary alcohol **20** in 72% yield, along with a small amount of regioisomer **21** (12%). Triflation of alcohol **20** followed by nucleophilic displacement of the resultant triflate with allylmagnesium bromide in the presence of CuBr[23] afforded elongated olefin **22** in 89% yield for the two steps. Oxidative removal of the PMB group of **22** with DDQ followed by oxidation of the derived secondary alcohol with tetra-*n*-propylammonium perruthenate (TPAP)/NMO[24] provided ketone **23** in 85% yield for the two steps. Subsequent treatment of ketone **23** with Me_3Al (CH_2Cl_2, −78 to −15 °C) delivered tertiary alcohol **24** in a highly stereoselective manner

Scheme 2. Synthesis of Lactone 12



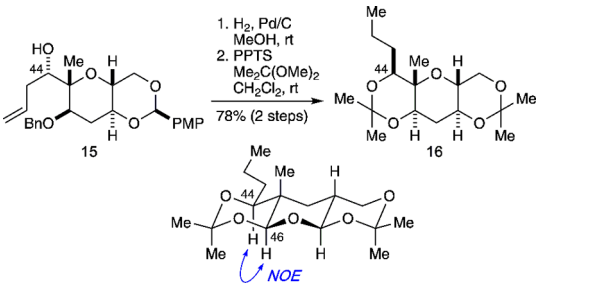


Figure 2. Stereochemical assignment of homoallylic alcohol **15**.

in 94% yield.[25] The configuration of the C48 stereogenic center of **24** was established by an NOE as shown. Hydroboration of the terminal olefin of **24** quantitatively provided diol **25**, which was subjected to 2-hydroxy-2-azaadamantane (AZADOL)-catalyzed oxidation in the presence of $PhI(OAc)_2$ (CH_2Cl_2/pH 7 buffer)[26] to yield carboxylic acid **26** in 88% yield. Finally, Yamaguchi lactonization[27] of hydroxy acid **26** completed the assembly of seven-membered lactone **12** in 95% yield.

With the synthetic route to lactone **12** in hand, we performed the hydroxymethylation by Stille coupling of the corresponding enol phosphate.[28] Thus, enolization of lactone **12** with KHMDS in the presence of $(PhO)_2P(O)Cl$ (HMPA, THF, −78 °C) afforded enol phosphate **11** (95%), which was unstable and immediately subjected to hydroxymethylation by Stille coupling with (tributylstannyl)methanol[19] (Scheme 3). Cross-coupling of enol phosphate **11** with (tributylstannyl)-

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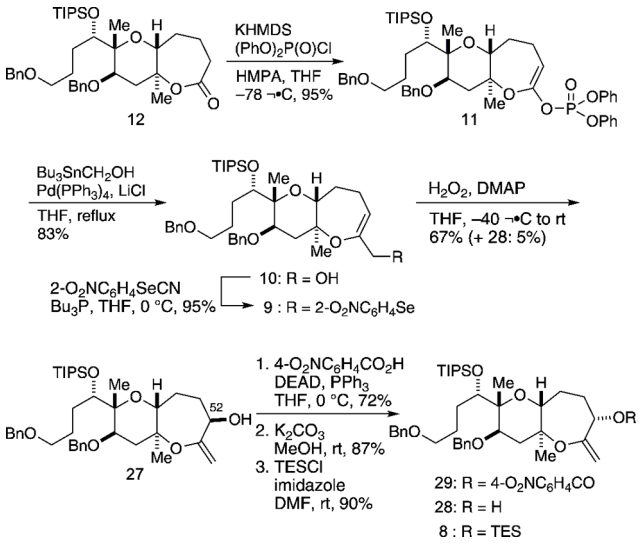
Scheme 3. Synthesis of *exo*-Enol Ether 8



methanol proceeded in the presence of $Pd(PPh_3)_4$ and LiCl (THF, reflux) to give allylic alcohol **10** in 83% yield. Alcohol **10** was subsequently transformed to 2-nitrophenyl selenide **9** in 95% yield by means of the Grieco–Nishizawa protocol.[29] Upon treatment of selenide **9** with an excess amount of 30% aqueous H_2O_2 solution in the presence of DMAP (5 equiv) in THF at −40 °C to room temperature, the seleno-Mislow–Evans rearrangement[18] proceeded smoothly to give α-hydroxy *exo*-enol ether **27** with the undesired configuration at C52 in 67% yield, along with a small amount of the desired epimer **28** (6%). The relative configuration of the C52 stereogenic center of **27** was established by NOE data as shown in Figure 3. The

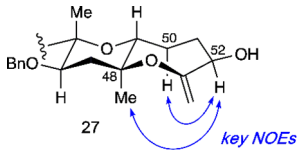
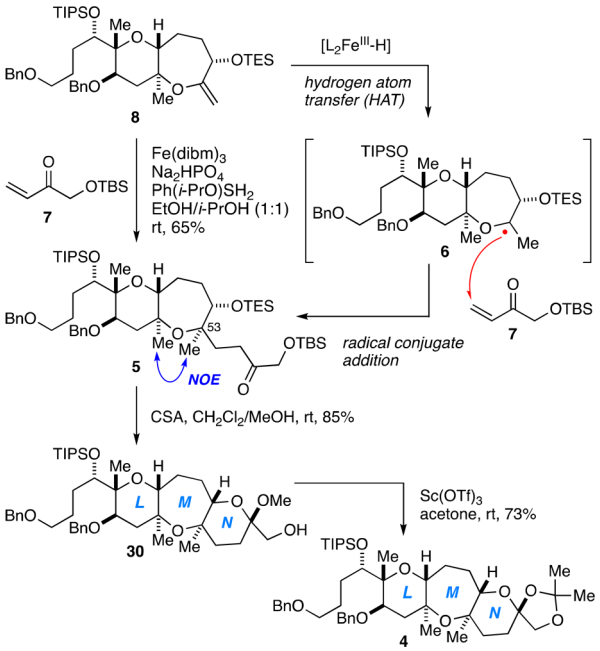


Figure 3. Stereochemical assignment of alcohol **27**.

observed stereoselectivity of this [2,3]-sigmatropic rearrangement could be ascribed to the steric hindrance of the angular methyl group at C48. Inversion of the C52 hydroxy group of **27** was performed using modified Mitsunobu conditions (4-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD, THF, 0 °C)[30] followed by methanolysis of the resulting 4-nitrobenzoate **29** (K_2CO_3, MeOH) to afford alcohol **28** in 63% yield for the two steps. Silyl protection of **28** using TESCl/imidazole in DMF led to TES ether **8** in 90% yield.

Having completed the synthesis of key intermediate **8**, we examined the crucial HAT-based reductive olefin coupling[15] with known vinyl ketone **7**[14] to generate the sterically congested tetrasubstituted stereogenic center at C53. After some experimentation, it was found that the use of (isopropoxy)phenylsilane (Ph(*i*-PrO)SiH_2)[31] as a reductant in the presence of iron(III) diisobutyrylmethanoate (Fe(dibm)$_3$)[15b,c] gave the best result. Thus, addition of Ph(*i*-PrO)SiH_2 (3 equiv) to vinyl ketone **7**[14] (3 equiv) and *exo*-enol ether **8** in the presence of Fe(dibm)$_3$ (10 mol %) and Na_2HPO_4 (1 equiv) in EtOAc/*i*-PrOH (1:1) at room temperature provided the desired cross-coupling product **5** in 65% yield as a single stereoisomer via the intermediacy of nucleophilic radical **6** (Scheme 4). The configuration of the

Scheme 4. Synthesis of LMN-Ring Fragment 4 of C-CTX-1



newly created tetrasubstituted stereogenic center at C53 was established by the observation of an NOE between two methyl groups as shown. The stereochemical outcome of this intermolecular radical conjugate addition could be explained by the effective shielding of the α-face of the seven-membered ether ring by the angular methyl and silyloxy substituents. To the best of our knowledge, this is the first example of the application of HAT-based reductive olefin cross-coupling to the elaboration of a functionalized seven-membered ether ring system. Selective deprotection of the TBS and TES groups of **5** was achieved under acidic conditions (CSA, CH_2Cl_2/MeOH) to give methyl acetal **30** in 85% yield. Finally, treatment of **30** with scandium(III) triflate[9a,32] in acetone completed the synthesis of the desired LMN-ring fragment **4** of C-CTX-1 in 73% yield.

In summary, we have developed an efficient synthetic route to the LMN-ring fragment of Caribbean ciguatoxin C-CTX-1. The key features of the synthetic route include a hydroxymethylation by Stille coupling of a seven-membered enol phosphate with (tributylstannyl)methanol, a [3,3]-sigmatropic rearrangement of the allylic selenoxide to construct the α-hydroxy *exo*-enol ether, and a HAT-based reductive olefin cross-coupling to access a sterically congested tetrasubstituted stereogenic center on the strained seven-membered M-ring with the pseudoaxially oriented 1,3-diaxial dimethyl structure in a highly stereoselective manner. Further studies aimed at the development of a synthetic route to the right wing of Caribbean ciguatoxin C-CTX-1 and its total synthesis are underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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