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An improved synthesis of the C42–C52 segment of ciguatoxin 3C

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ABSTRACT

In our previously reported method for the construction of the IJKLM-ring of ciguatoxin 3C (CTX3C), the lengthy synthetic process for the intermediate C42–C52 (L-ring) segment was problematic. Therefore, a new and improved procedure for the C42–C52 segment, having modified protecting groups, was developed. The new route includes a chirality transferring Ireland-Claisen rearrangement for the construction of the vicinal dimethyl branching at C47–48, a one-pot cyclization process for the establishment of the stereocenters at C45 and C46 as well as the γ-hydroxy δ-lactone framework corresponding to the L-ring, and Brown's asymmetric crotylboration for the installation of the stereocenters at C43 and C44. The new C42–C52 segment was successfully coupled with the previously reported C32–C41 (I-ring) segment to produce the IJKLM-ring.

Ciguatoxin 3C (CTX3C) (**1**) (Fig. 1) was isolated from cultured dinoflagellate *Gambierdiscus toxicus* as one of the causative toxins of ciguatera fish poisoning, which often breaks out in tropical and subtropical coral leaf regions causing serious nervous system disorders in patients.[1,2] The ciguatera toxins including **1** have a ladder-shaped, fused polycyclic ether framework typically including 13 ether rings with 30 or more stereocenters. The complex molecular structure and the strong neurotoxicity of the ciguatera toxins have attracted considerable attention from synthetic chemists, and, therefore, many studies toward the total synthesis of **1** and its congeners have been conducted.[3–6] However, to date, only the Hirama[4] and the Isobe[5] groups have achieved the total synthesis of the ciguatera toxins.

During the course of our investigations toward the total synthesis of **1**,[6] we have synthesized the ABCDEF-ring and the IJKLM-ring segments[6b,c,g] and developed a method for the construction of the FGHI-ring from the F- and I-ring segments as a prototype for the final steps of the total synthesis of **1**.[6d] However, in the synthesis of the IJKLM-ring, the lengthy synthetic process (3.9% over 30 steps from tri-*O*-acetyl-D-glucal) for the intermediate C42–C52 (L-ring) segment caused difficulty in large-scale synthesis.[6b] Therefore, a new pathway for the C42–C52 segment was explored. Here, we describe the successful synthesis of a new C42–C52 segment, having modified protecting groups, with a reduced number of reactions compared to that of the previous route.

We planned a convergent synthesis of the IJKL-ring **2** from I-ring **3** and newly designed the C42–C52 segment **4** as shown in Scheme 1. Due to the expected instability of the LM-ring of **1**, the spiroacetal was intended to be constructed at the final stage of the total synthesis from an intermediate having a stable cyclic ether corresponding to the L-ring. Therefore, oxane **4** was employed as the stable L-ring segment, which would be connected to I-ring **3** to form IJKL-ring **2** by our previously developed method. Since the previous C42–C52 segment had issues of unfavorable detachment of the protecting group at O52 during the formation of the J- and K-rings, we replaced the protecting group with a stable 4-methoxyphenyl (PMP) group. For the protecting group of the oxygen atom at C44, a 4-bromobenzyl (PBB) group was selected based on stability and removability under specific conditions.[7] The PMP and PBB groups would be removed at the final stage of the total synthesis. The 4-(methylphenylamino)benzyl (PMPAB) group at O46 was employed as a temporary protecting group, which would be removed before the K-ring formation.[7] Thus, compound **4** was designed as the new C42–C52 segment.

The plan for the construction of **4** is shown in Scheme 2. Aldehyde **4** would be derived by oxidative cleavage of alkene **5**, in which the C43 and C44 stereocenters would be established by Brown's asymmetric crotylboration of **6**.[8] The installation of the C50–C52 unit and the PBB group to lactone **7** would produce **6**. The construction of the stereocenters at C45 and C46 of **7** would rely on a process including transformation of the 2,2-dimethyl-

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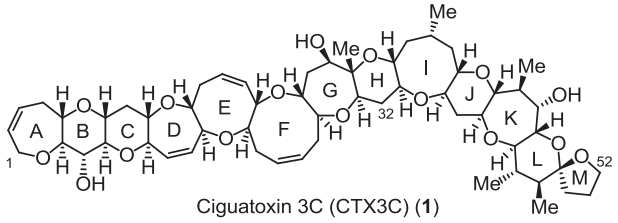
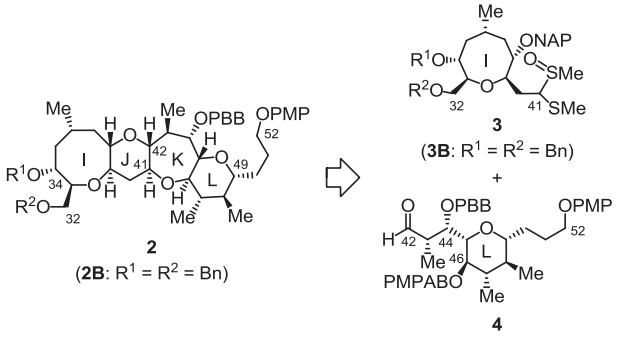
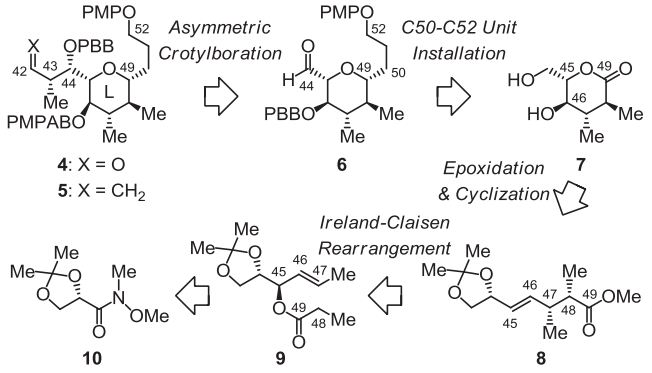


Fig. 1. The structure of ciguatoxin 3C (**1**).



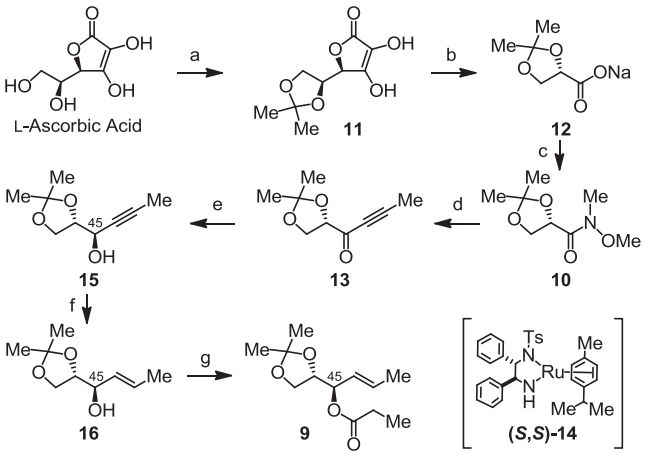
Scheme 1. Plan for the construction of IJKL-ring **2**. PMP: 4-methoxyphenyl; PBB: 4-bromobenzyl; NAP: 2-naphthylmethyl; PMPAB: 4-(methylphenylamino)benzyl.



Scheme 2. Plan for the synthesis of C42–C52 segment **4**. PMP: 4-methoxyphenyl; PMPAB: 4-(methylphenylamino)benzyl; PBB: 4-bromobenzyl.

1,3-dioxolane moiety of **8** to a hydroxymethyl group, asymmetric epoxidation of the double bond at C45 and C46, and 5-*exo* cyclization of the resulting epoxy ester to form a γ-lactone. The resulting γ-lactone was expected to be transformed to stable δ-lactone **7**, in which all the four substituents are equatorial.[9] Establishment of the *syn*-dimethyl group with (47*R*,48*S*)-configuration in **8** employed chirality-transferring Ireland-Claisen rearrangement of ester **9**, which would be prepared from chiral Weinreb amide **10**.

The synthesis of **9** via **10** is illustrated in Scheme 3. Weinreb amide **10** was prepared from L-ascorbic acid through a three-step process as follows: (i) formation of isopropylidene ketal **11** (98%),[10] (ii) oxidative cleavage of **11** by Carlsen's procedure[11] with some modifications[12] to give protected glycerate salt **12**, and (iii) amidation of **12** with *N*,*O*-dimethylhydroxylamine in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) to produce **10** (85% over 2 steps). Weinreb amide **10** was reacted with 1-propynylmagnesium bromide to afford ketone **13** (90%).[13] Although several successful examples were reported for the diastereoselective reduction of 2,2-dimethyl-1,3-dioxolan-4-yl ketones,[14,6e] ketone **13** was only reduced with low diastereoselectivity even after intensive exploration of reaction conditions using achiral reductants. Therefore,



Scheme 3. Synthesis of ester **9**. Reagents and conditions: (a) 2,2-dimethoxypropane, PTS·H_2O (cat.), acetone, 20 °C, 2 h, 98%; (b) 2 mol/L aq. NaOH, 2 mol/L aq. NaClO, RuO_2·H_2O (cat.), 40 °C, 1 h; (c) MeN(H)OMe·HCl, DCC, DMAP (cat.), CH_2Cl_2, 25 °C, 3 h, 85% from **11**; (d) 1-propynylmagnesium bromide, THF, −20 °C, 30 min, 90%; (e) formic acid, Et_3N, **(*S*,*S*)-14** (cat.), Et_2O, 25 °C, 3 h, 83% (**15**:***epi*-15** = 17:1); (f) $LiAlH_4$, THF, 40 °C, 5 h, 95%; (g) propanoyl chloride, pyridine, DMAP (cat.), CH_2Cl_2, 24 °C, 8 h, 99%. PTS: *p*-toluenesulfonic acid; DCC: *N*,*N*′-dicyclohexylcarbodiimide; DMAP: 4-dimethylaminopyridine.

the asymmetric reduction of **13** was examined with ruthenium catalyst **(*S*,*S*)-14** under Noyori conditions.[15] As a result, desired (*R*)-alcohol **15** was produced in 83% yield with high stereoselectivity (**15**:***epi*-15** = 17:1). Interestingly, the enantiomer of **13** (***ent*-13**) gave (*R*)-alcohol ***ent-epi*-15** with lower stereoselectivity (***ent*-15**: ***ent-epi*-15** = 1:7) under the same reduction conditions using **(*S*,*S*)-14**, thereby indicating that the 2,2-dimethyl-1,3-dioxolane moiety of **13** has matched stereochemistry with **(*S*,*S*)-14** in the Noyori reduction. Upon treatment with $LiAlH_4$, propargyl alcohol **15** was converted to (*E*)-allyl alcohol **16** (95%), which was esterified with propanoyl chloride to give ester **9** (99%). The (*R*)-configuration of the C45 stereocenter of the product was confirmed by NMR analysis using (*R*)- and (*S*)-Mosher esters of **16**.[16]

Lactone **7** was constructed from ester **9** as shown in Scheme 4. First, ester **9** was subjected to Ireland-Claisen rearrangement. After intensive explorations, we found the following optimized conditions: treatment of **9** with KDA, prepared by the mixing of LDA and Tf_2NK in THF-HMPA (3:1) at −40 °C for 5 min, and TMSCl at −78 °C for 30 min followed by warming to ambient temperature gave a rearranged product, which was esterified with $TMSCHN_2$ to afford a 6:1 inseparable mixture of **8** and **α-*epi*-8** in 88% combined yield from **9**. The standard conditions using LDA in THF gave **8** and **α-*epi*-8** in 79% yield with low selectivity (1:1), while the use of sodium bis(trimethylsilyl)amide (NHMDS) in THF-HMPA (2:1) produced **8** selectively (**8**:**α-*epi*-8** = >10:1) but in low yield (<30%). The undesired, minor α-epimer could not be separated from the desired major stereoisomer until the stage of lactone formation. Upon treatment in one-pot with aqueous HCl followed by $NaIO_4$, the 6:1 mixture of **8** and **α-*epi*-8** was converted to a diastereomeric mixture of aldehydes, which was reduced under Luche conditions[17] to produce a 6:1 mixture of **18** and **α-*epi*-18** (98% over 3 steps). The mixture of allyl alcohols was stereoselectively transformed to a 6:1 mixture of **19** and **α-*epi*-19** by Sharpless asymmetric epoxidation using L-(+)-DIPT (78%).[18] When the mixture of epoxides was heated in refluxing H_2O, the formation of γ-lactones (**20** and **α-*epi*-20**) by 5-*exo* epoxide ring opening was observed. Next, the reaction solution was basified in situ with NaOH to produce hydrolyzed **21** and **α-*epi*-21**, which were cyclized in situ by acidification of the solution with HCl to give lactones **7** and **α-*epi*-7**. Because lactone **7** was obtained as crystals, recrystallization was effective to separate **7** from **α-*epi*-7**. The