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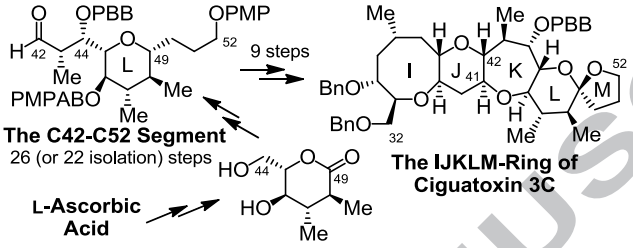

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An improved synthesis of the C42-C52 segment of ciguatoxin 3C

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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**) (Figure 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.[3,4,5,6] However, to date, only the Hirama[4] and the Isobe[5] groups have achieved the total synthesis of the ciguatera toxins.

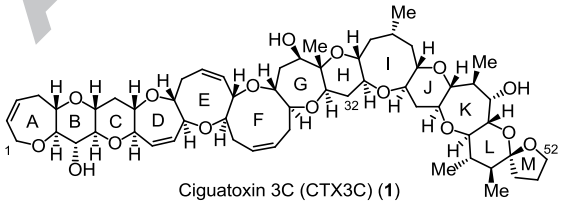

Figure 1. The structure of ciguatoxin 3C (**1**).

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.

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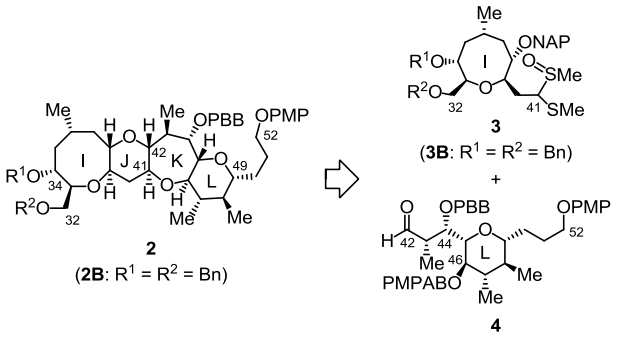
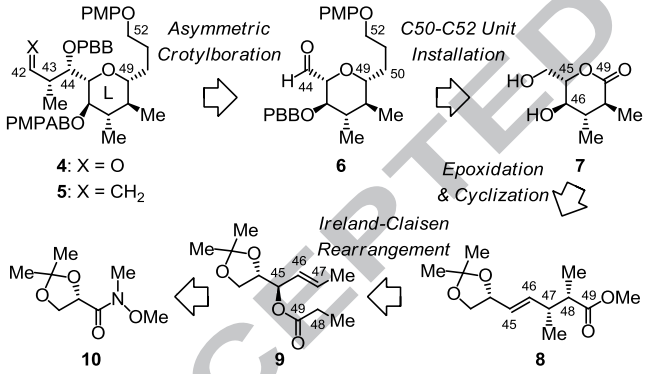


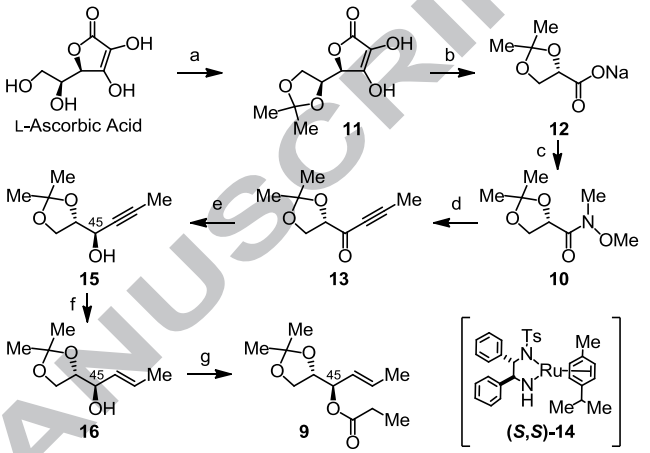
Scheme 1. Plan for the construction of IJKL-ring **2**. PMP: 4-methoxyphenyl; PBB: 4-bromobenzyl; NAP: 2-naphthylmethyl; PMPAB: 4-(methylphenylamino)benzyl.

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-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**.



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

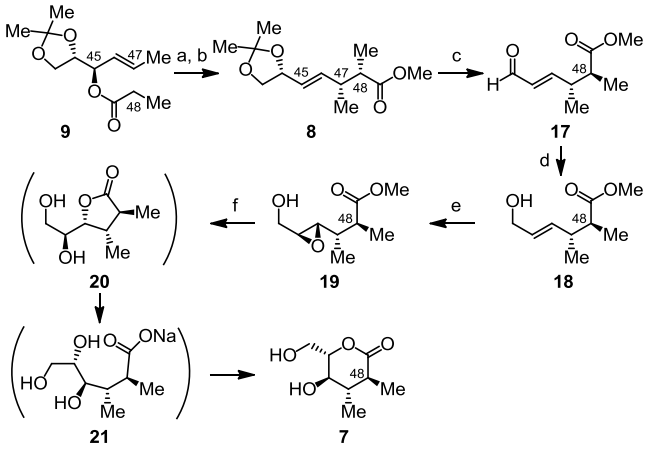
The synthesis of **9** via **10** is illustrated in Scheme 3. Weinreb amide **10** was prepared from L-ascorbic acid through a three-step process as follows: (i) formation of isopropylidene ketal **11** (98%),[10] (ii) oxidative cleavage of **11** by Carlsen's procedure[11] with some modifications[12] 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, 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]



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.

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 stereostructure of **7** was confirmed by X-ray crystallographic analysis (Figure 2).[19] Thus, lactone **7** was obtained in 66% yield from the 6:1 mixture of **19** and ***α-epi*-19** through a one-pot three-step process, achieved by simple heating, basification, and acidification in aqueous media.



Scheme 4. Synthesis of lactone **7**. Reagents and conditions: (a) *i*-Pr_2NH, Tf_2NK, BuLi, –40 °C, THF-HMPA (3:1), 5 min, then **9**, TMSCl, THF-HMPA (2:1), –78 °C, 30 min, then 24 °C, 3.5 h; (b) $TMSCHN_2$, MeOH-PhH (1:1), 24 °C, 20 min, 88% (an inseparable 6:1 mixture of **8** and ***α-epi*-8**) from **9**; (c) 2 mol/L aq. HCl, THF, 24 °C, 3 h, then pH 7 buffer, $NaIO_4$, 0 → 24 °C, 1 h; (d) $NaBH_4$, $CeCl_3·7H_2O$, MeOH, –78 °C, 30 min, 98% (an inseparable 6:1 mixture of **18** and ***α-epi*-18**) from the above mixture of **8** and ***α-epi*-8**; (e) L-(+)-DIPT, Ti(O*i*-Pr)$_4$, TBHP, MS4A, CH_2Cl_2, –20 °C, 18 h, 78% (an inseparable 6:1 mixture of **19** and ***α-epi*-19**); (f) H_2O, reflux, 11 h, then 2 mol/L aq. NaOH, 24 °C, 6 h, then 12 mol/L aq. HCl, 24 °C, 2 h, then recrystallization, 66% (**7**) from the above mixture of **19** and ***α-epi*-19**. Tf: trifluoromethanesulfonyl; TMS: trimethylsilyl; HMPA: hexamethylphosphoric triamide; DIPT: diisopropyl tartrate; TBHP: *tert*-butyl hydroperoxide.

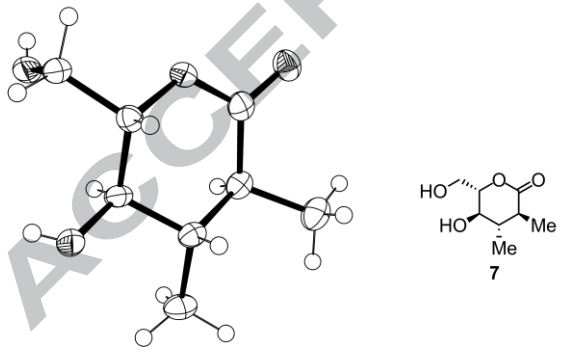
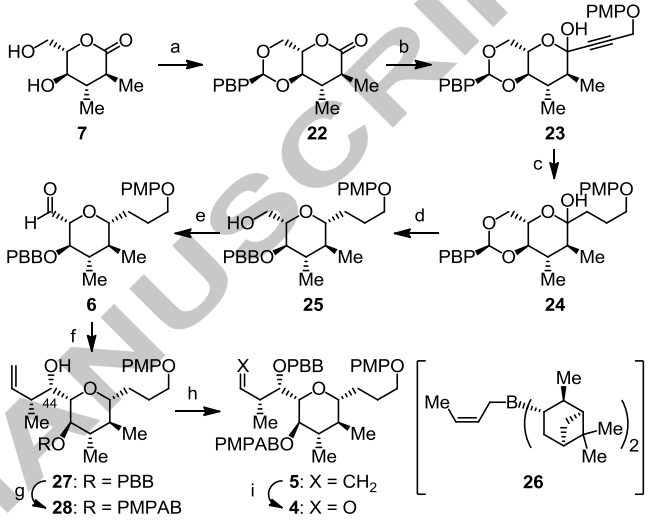


Figure 2. ORTEP diagram of **7**.

Next, lactone **7** was converted to L-ring segment **4** (Scheme 5). After protection of **7** as a cyclic 4-bromobenzylidene acetal (100%), the resulting lactone **22** was reacted with a lithium acetylide, derived from 3-(4-methoxyphenyloxy)prop-1-yne, to afford **23** (92%), which was hydrogenated with Wilkinson's catalyst to produce **24** (95%). Upon treatment of **24** with Et_3SiH in the presence of $PhBCl_2$ as a Lewis acid, the regioselective reductive cleavage of the cyclic acetal group and the stereoselective reduction of the hemiacetal group were simultaneously accomplished to give **25** (81%).[20] Oxidation of **25** with Dess-Martin periodinane (DMPI)[21] followed by Brown's asymmetric crotylboration using **26** produced **27** stereoselectively (72% over 2 steps).[8] The absolute configuration of **27** was determined by X-ray crystallographic analysis on 3,5-dinitrobenzoyl ester **29**, derived from **27** (Figure 3).[22,23] The PBB group of **27** was converted to the PMPAB group according to the Buchwald-Seeberger procedure (71%).[7] The resulting **28** was protected with PBBBr to give **5** (75%), the vinyl group of which was then transformed to a formyl group by a one-pot dihydroxylation/oxidative cleavage process to afford **4** (93%).[24] Thus, L-ring segment **4** was synthesized in 6.6% yield over 26 (or 18 isolation/purification) steps from L-ascorbic acid.



Scheme 5. Synthesis of C42-C52 segment **5**. Reagents and conditions: (a) 4-bromobenzaldehyde dimethylacetal, CSA (cat.), CH_2Cl_2, reflux, 30 min, 100%; (b) 3-(4-methoxyphenyloxy)prop-1-yne, BuLi, THF, –70 °C, 30 min, then **22**, –70 °C, 10 min, 92%; (c) H_2, $(Ph_3P)_3RhCl$ (cat.), PhH, 25 °C, 19 h, 95%; (d) Et_3SiH, $PhBCl_2$, –78 °C, 40 min, 81%; (e) DMPI, $NaHCO_3$, CH_2Cl_2, 25 °C, 1 h; (f) **26**, THF, –78 °C, 1 h, 72% from **25**; (g) PhN(H)Me, *t*-BuONa, (2-biphenyl)P(*t*-Bu)$_2$, Pd(OAc)$_2$ (cat.), THF, 25 °C, 3 d, 71%; (h) *t*-BuOK, Bu_4NI (cat.), PBBBr, THF, 25 °C, 16 h, 75%; (i) OsO_4 (cat.), NMO, pH 7 buffer, 1,4-dioxane, 25 °C, 11.5 h, then $NaIO_4$, 24 °C, 1 h, 93%. CSA: 10-camphorsulfonic acid; DMPI: Dess-Martin periodinane; NMO: *N*-methylmorpholine *N*-oxide.

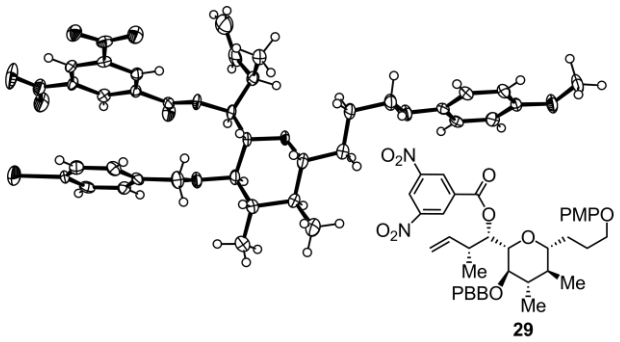
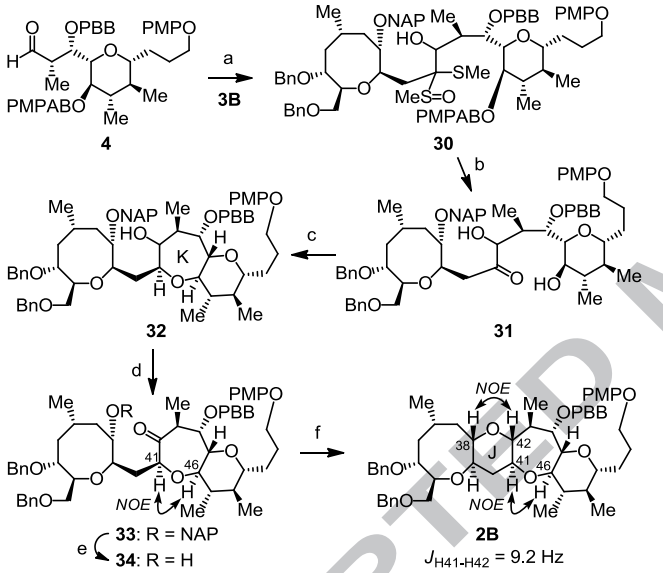


Figure 3. ORTEP diagram of 3,5-dinitrobenzoyl ester **29**.

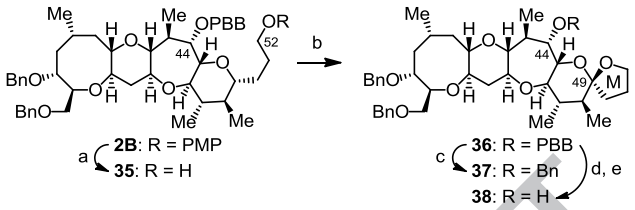
With L-ring segment **4** in hand, we examined the connection of **4** with I-ring segment **3B**[6c] followed by JK-ring formation (Scheme 6). Although the Bn groups of **3B** are inappropriate for further synthesis due to the difficulty in their selective removal in the presence of the PBB ether after completion of the IJKL-ring synthesis, we used **3B** as a good model compound to demonstrate the function of the protecting groups of **4** during the

transformation to the IJKL-ring **2B**. First, dithioacetal mono-*S*-oxide **3B** was deprotonated with LDA, and the resulting anion was reacted with aldehyde **4** to give adduct **30** (72%).[6c,25] Upon treatment of **30** with *p*-toluenesulfonic acid (PTS) in MeOH, the dithioacetal mono-*S*-oxide moiety and the PMPAB group were hydrolyzed to give ketodiol **31** (65%). Reductive etherification of **31** with Et_3SiH in the presence of TMSOTf afforded tricyclic ether **32**,[26] which was subjected to Swern oxidation to produce ketone **33** as a single diastereomer (87% over 2 steps).[27] The stereochemistry at C41 was determined by NMR analysis, in which the NOE enhancement between H41 and H46 was observed. After the NAP group of **33** was removed by DDQ,[28] the resulting **34** was cyclized with Et_3SiH and TMSOTf to furnish tetracyclic **2B** (79% over 2 steps).[29] The *trans*-fusion between the J- and K-rings was confirmed by the presence of NOE correlations between H38/H42 and between H41/H46 as well as a large $^3J_{H41\text{-}H42}$ value (9.2 Hz). Thus, the connection of L-ring **4** with I-ring **3B** followed by JK-ring formation smoothly proceeded in 6 steps to produce **2B** in 32% overall yield without any problem with the protecting groups.



Scheme 6. Synthesis of IJKL-ring **2B**. Reagents and conditions: (a) **3B**, LDA, THF, –20 °C, 10 min, then **4**, –78 °C, 1.5 h, 72%; (b) PTS·H_2O (cat.), MeOH, CH_2Cl_2, 24 °C, 13 h, 65%; (c) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 10 min; (d) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 → 0 °C, 20 min, 87% from **31**; (e) DDQ, H_2O-CH_2Cl_2 (1:10), 25 °C, 1.5 h; (f) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 10 min, 79% from **33**. NOE: nuclear Overhauser effect.

Finally, formation of the LM-ring and detachment of the PBB group at O44, which were scheduled for the final stage of our total synthesis of CTX3C, were demonstrated (Scheme 7). The PMP group of **2B** was removed with cerium(IV) ammonium nitrate (CAN) to give alcohol **35** (86%).[30] Treatment of **35** with $PhI(OAc)_2$ and iodine under photoirradiation with a 60 W incandescent lamp afforded a 1:1 mixture of spiroacetal **36**[31] and its C49 epimer.[32] The epimer was isomerized with 10-camphorsulfonic acid (CSA) in MeOH to give **36** as a single stereoisomer (78%).[33,6c] The stereochemistry of the spiroacetal moiety was confirmed by the transformation of **36** under basic conditions to known **37** (89%), which was previously synthesized by the Hirama group[34] and ours.[6c] The removal of the PBB group of **36** was also tested. The amination of the PBB group with *N*-methylaniline in the presence of a palladium catalyst followed by the acidic removal of the resulting PMPAB ether produced **38**[35] (69% over 2 steps).[7] This strongly suggests that the PMP group at O52 and the PBB group at O44 would properly function as protecting groups in the total synthesis of CTX3C.



Scheme 7. Formation of the LM-ring and conversion of the PBB ether at C44. Reagents and conditions: (a) CAN, MeCN-CH_2Cl_2-H_2O (2:1:2), 0 °C, 30 min, 86%; (b) $PhI(OAc)_2$, I_2, *hν*, cyclohexane, 23 °C, 3 h, then CSA, MeOH-CH_2Cl_2 (1:1), 23 °C, 24 h, 78%; (c) BuLi, THF, –78 °C, 1 h, then H_2O, –78 → 23 °C, 1 h, 89%; (d) PhN(H)Me, *t*-BuONa, (2-biphenyl)P(*t*-Bu)$_2$, $Pd(dba)_3$·$CHCl_3$ (cat.), PhMe, 80 °C, 16 h; (e) CSA, MeOH-CH_2Cl_2 (1:1), 40 °C, 1 h, 69% from **36**. CAN: cerium(IV) ammonium nitrate; dba: dibenzylideneacetone.

In conclusion, an improved process for the C42-C52 segment (**4**) of CTX3C, having modified protecting groups, was developed. The new route includes 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 process, which produced **4** in 6.6% yield over 26 steps from L-ascorbic acid, was also simplified by the omission of 8 isolation/purification steps, thereby requiring only 18 isolation/purification steps from L-ascorbic acid. Thus, the present synthesis of **4** is clearly improved as compared to the previous synthesis, which provided the same part in 3.9% yield over 30 (or 26 isolation/purification) steps from tri-*O*-acetyl-D-glucal. The new C42-C52 segment (**4**) was successfully coupled to the previously reported C32-C41 (I-ring) segment (**3B**) to produce the IJKLM-ring. Further studies toward the total synthesis of ciguatoxin CTX3C are now in progress in this laboratory.

Acknowledgments

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19. Crystal data of **7**: Crystals were obtained by recrystallizing from EtOAc. $C_8H_{14}O_4$, M = 174.20, colorless platelet, 0.60 × 0.30 × 0.2 mm^3, monoclinic $P2_1$ (No. 4), a = 6.1339(7) Å, b = 9.462(2) Å, c = 7.4988(13) Å, β = 90.428(10)°, V = 435.23(14) $Å^3$, D_c (Z = 2) = 1.329 g cm^{-3}. A total 1546 unique data ($2\theta_{max}$ = 52°) were measured at T = 150 K by Rigaku Mercury 70 apparatus (Mo Kα radiation, λ = 0.71075 Å). Numerical absorption correction was applied (μ = 1.06 cm^{-1}). The structure was solved by the direct method (SIR2004) and refined by the full-matrix least-squares method of F^2 with anisotropic temperature factors for non-hydrogen atoms (SHELXL97). All the hydrogen atoms were located at the positions inferred from neighboring sites, and treated by a mixture of independent and constrained refinement. The final *wR* value is 0.1100 (all data) for 1546 reflections and 118 parameters. CCDC 1584173.
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22. Crystal data of **29**: Crystals were obtained by recrystallizing from hexane-EtOAc. $C_{36}H_{41}N_2O_{10}Br$, M = 741.63, orange block, 0.50 × 0.15 × 0.15 mm^3, monoclinic $P2_1$ (No. 4), a = 14.190(4) Å, b = 5.9505(15) Å, c = 22.708(6) Å, β = 108.087(4)°, V = 1822.7(9) $Å^3$, D_c (Z = 2) = 1.351 g cm^{-3}. A total 7600 unique data ($2\theta_{max}$ = 55°) were measured at T = 150 K by Rigaku Mercury 70 apparatus (Mo Kα radiation, λ = 0.71075 Å). Numerical absorption correction was applied (μ = 11.89 cm^{-1}). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method of F^2 with anisotropic temperature factors for non-hydrogen atoms (SHELXL97). All the hydrogen atoms were located at the positions inferred from neighboring sites, and treated by constrained refinement. The final *wR* value is 0.056 (all data) for 7600 reflections and 443 parameters. The absolute structure was deduced based on Flack parameter, 0.000(5), refined using 3079 Friedel pairs. CCDC 1584171.
23. The absolute stereochemistry of **27** was verified by the Kusumi-Mosher analysis on (*R*)- and (*S*)-MTPA esters of **27**,[16] which showed the (*S*)-configuration of C44.
24. Spectral data of **4**: $[\alpha]_D^{26}$ –4.65 (*c* 1.31, $CHCl_3$); IR (neat) ν 2967, 2929, 2875, 1721, 1595, 1508, 1466, 1342, 1303, 1231, 1181, 1106, 1071, 1043, 1012, 824, 806, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS as 0.00 ppm) δ 0.87 (3H, d, J = 6.5 Hz), 1.10-1.21 (1H, m), 1.12 (3H, d, J = 6.3 Hz), 1.25 (3H, d, J = 7.2 Hz), 1.35-4.53 (2H, m), 1.74-2.01 (3H, m), 2.83 (1H, brdq, J = 5.3, 7.2 Hz), 2.96 (1H, t, J = 9.8 Hz), 3.01 (1H, brt, J = 9.0 Hz), 3.30 (3H, s), 3.57 (1H, dd, J = 1.2, 9.7 Hz), 3.76 (3H, s), 3.93 (2H, t, J = 6.0 Hz), 4.07 (1H, brdd, J = 1.2, 5.3 Hz), 4.42 (1H, d, J = 12.1 Hz), 4.51 (2H, s), 4.58 (1H, d, J = 12.1 Hz), 6.78-6.85 (4H, m), 6.95 (2H, d, J = 8.4 Hz), 6.98 (1H, brt, J = 7.5 Hz), 7.03 (2H, brd, J = 8.4 Hz), 7.14 (2H, d, J = 8.3 Hz), 7.16 (2H, d, J = 8.4 Hz), 7.27 (2H, brdd, J = 7.5, 8.4 Hz), 7.40 (2H, d, J = 8.3 Hz), 9.72 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$, $^{13}CDCl_3$ as 77.0 ppm) δ 10.7 (CH_3), 14.3 (CH_3), 15.5 (CH_3), 25.2 (CH_2), 29.4 (CH_2), 40.2 (CH_3), 41.4 (CH), 44.1 (CH), 47.8 (CH), 55.7 (CH_3), 68.5 (CH_2), 71.2 (CH_2), 73.8 (CH_2), 78.2 (CH), 80.7 (CH), 81.7 (CH), 82.2 (CH), 114.6 (CH × 2), 115.4 (CH × 2), 119.8 (CH × 2), 121.0 (CH × 2), 121.3 (C), 121.7 (CH), 129.0 (CH × 2), 129.22 (CH × 2), 129.23 (CH × 2), 130.3 (C), 131.4 (CH × 2), 137.5 (C), 148.77 (C), 148.84 (C), 153.2 (C), 153.6 (C), 204.1 (CHO); FD-HRMS (*m/z*) calcd for $C_{42}H_{50}{}^{79}BrNO_6$ [M^+]: 743.2822, found: 743.2833.
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29. Spectral data of **2B**: $[\alpha]_D^{27}$ –2.35 (*c* 1.16, $CHCl_3$); IR (neat) ν 3063,3030, 2954, 2926, 2869, 1508, 1488, 1453, 1368, 1336, 1287, 1231, 1096, 1073, 1011, 910, 823, 804, 736, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, $C_6\underline{H}D_5$ as 7.15 ppm) δ 0.71 (3H, d, J = 6.4 Hz), 1.01 (3H, d, J = 7.0 Hz), 1.02-1.15 (1H, m), 1.13 (3H, d, J =

7.6 Hz), 1.18 (3H, d, *J* = 5.9 Hz), 1.16-1.28 (1H, m), 1.40-1.50 (1H, m), 1.54-1.62 (1H, m), 1.70-1.84 (4H, m), 1.85-2.01 (3H, m), 2.04 (1H, brd, *J* = 13.8 Hz), 2.36-2.44 (1H, m), 2.70-2.77 (1H, m), 2.86 (1H, brdt, *J* = 1.9, 8.9 Hz), 3.04 (1H, dd, *J* = 4.7, 9.2 Hz), 3.14-3.20 (1H, m), 3.27 (1H, brd, *J* = 9.1 Hz), 3.28-3.36 (1H, m), 3.34 (3H, s), 3.32-3.40 (1H, m), 3.46-3.53 (1H, m), 3.55 (1H, brt, *J* = 9.3 Hz), 3.60 (1H, brd, *J* = 2.3 Hz), 3.65-3.72 (2H, m), 3.77 (2H, t, *J* = 6.2 Hz), 4.07 (1H, brddd, *J* = 5.2, 9.2, 11.3 Hz), 4.11 (1H, d, *J* = 11.6 Hz), 4.40 (1H, d, *J* = 11.6 Hz), 4.40 (2H, s), 4.51 (2H, s), 6.78 (2H, d, *J* = 9.0 Hz), 6.86 (2H, d, *J* = 9.0 Hz), 7.07-7.23 (10H, m), 7.30-7.35 (4H, m); ^{13}C NMR (125 MHz, C_6D_6, $^{13}\underline{C}C_5D_6$ as 128.0 ppm) δ 14.4 (CH_3), 15.9 (CH_3), 20.2 (CH_3), 25.7 (CH_2), 26.6 (CH_3), 28.6 (CH), 29.9 (CH_2), 39.3 (CH_2), 40.4 (CH_2), 40.8 (CH), 41.5 (CH), 42.7 (CH), 44.4 (CH_2), 55.2 (CH_3), 68.6 (CH_2), 71.3 (CH_2), 71.8 (CH_2), 72.8 (CH_2), 73.3 (CH_2), 74.8 (CH), 78.5 (CH), 79.6 (CH), 80.2 (CH), 81.2 (CH), 82.2 (CH), 82.5 (CH), 85.3 (CH), 85.6 (CH), 87.6 (CH), 115.0 (CH × 2), 115.7 (CH × 2), 121.5 (C), 127.5 (CH), 127.6 (CH), 127.7 (CH × 2), 127.9 (CH × 2), 128.48 (CH × 2), 128.49 (CH × 2), 129.7 (CH × 2), 131.6 (CH × 2), 138.7 (C), 139.2 (C), 139.4 (C), 153.8 (C), 154.4 (C); FD-HRMS (*m/z*) calcd for $C_{53}H_{67}{}^{79}BrO_9$ [M^+]: 926.3968, found: 926.3960.

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35. Spectral data of **38**: $[\alpha]_D{}^{24}$ –18.3 (*c* 0.109, $CHCl_3$); IR (neat) *ν* 3461, 3060, 3029, 2923, 2852, 1730, 1656, 1602, 1515, 1496, 1454, 1374, 1330, 1286, 1261, 1177, 1102, 1073, 1026, 976, 942, 868, 845, 805, 748, 699 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, $C_6\underline{H}D_5$ as 7.15 ppm) δ 0.87 (3H, d, *J* = 6.7 Hz), 1.00 (3H, d, *J* = 7.1 Hz), 1.16 (3H, d, *J* = 6.3 Hz), 1.17 (3H, d, *J* = 7.5 Hz), 1.30-1.48 (2H, m), 1.54-1.64 (1H, m), 1.64-1.80 (5H, m), 1.84-1.93 (4H, m), 2.01 (1H, brtd, *J* = 2.5, 13.9 Hz), 2.32-2.39 (1H, m), 2.72 (1H, brtd, *J* = 4.8, 12.3 Hz), 2.99 (1H, dd, *J* = 5.6, 9.3 Hz), 3.12 (1H, dt, *J* = 2.9, 9.4 Hz), 3.25-3.43 (3H, m), 3.47-3.56 (1H, m), 3.64-3.75 (4H, m), 3.77 (1H, brs), 3.88 (1H, brdd, *J* = 1.4, 9.4 Hz), 3.93 (1H, ddd, *J* = 5.1, 9.3, 11.2 Hz), 4.12 (1H, d, *J* = 11.5 Hz), 4.41 (1H, d, *J* = 11.5 Hz), 4.42 (2H, s), 7.06-7.25 (8H, m), 7.35 (2H, brd, *J* = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, $^{13}\underline{C}DCl_3$ as 77.0 ppm) δ 13.4 (CH_3), 15.7 (CH_3), 19.7 (CH_3), 24.3 (CH_2), 26.7 (CH_3), 28.1 (CH), 34.9 (CH_2), 38.5 (CH), 39.5 (CH_2), 39.9 (CH_2), 42.1 (CH), 42.2 (CH), 44.2 (CH_2), 67.6 (CH_2), 71.4 (CH_2), 71.7 (CH), 72.1 (CH_2), 73.4 (CH_2), 75.7 (CH), 77.2 (CH), 78.6 (CH), 79.0 (CH), 80.6 (CH), 82.7 (CH), 85.5 (CH), 86.4 (CH), 108.7 (C), 127.4 (CH), 127.60 (CH), 127.61 (CH × 2), 127.9 (CH × 2), 128.29 (CH × 2), 128.33 (CH × 2), 138.3 (C), 138.5 (C); FD-HRMS (*m/z*) calcd for $C_{39}H_{54}O_8$ [M^+]: 650.3819, found: 650.3809.

Development of a practical synthetic route to the C42-C52 segment of ciguatoxin 3C

Stereoselective construction of the vicinal dimethyl branching at C47-48 by chirality transferring Ireland-Claisen rearrangement

Stereoselective formation of a γ-hydroxy δ-lactone from an epoxy ester by a one-pot, three-step cyclization process