CONVERGENT STRATEGY FOR SYNTHESIZING POLYCYCLIC ETHER MARINE TOXINS: SYNTHESIS OF THE ABCDE RING FRAGMENT OF CIGUATOXIN CTX3C

Megumi Maruyama, Kenji Maeda, Tohru Oishi, Hiroki Oguri, and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, and CREST, Japan Science and Technology Corporation (JST), Sendai 980-8578, Japan
E-mail: hirama@ykbsc.chem.tohoku.ac.jp

Abstract - The ABCDE ring fragment of CTX3C, the most important member of the ciguatoxin family, was concisely synthesized by extensive use of ring-closing olefin metathesis.

Ciguatoxin (CTX1B, 1) and its congener, CTX3C (2), which possess gigantic structure and unique agonist activity against the sodium channel, are the principal toxin that causes ‘ciguatera’ seafood poisoning.1 During the course of our synthetic studies into ciguatoxins,2,3 we have recently succeeded in synthesizing the ABCDE ring framework4 of 1 based on alkylation and ring-closing metathesis (RCM).5 We describe herein a convergent synthesis of the ABCDE ring fragment (3) of 2.

‡ Dedicated to Professor Shô Itô on occasion of his 77th birthday
Our hypothesis was to use RCM extensively for constructing seven- and eight-membered ring systems of 3 (Scheme 1). A precursor (4) of 3 would be prepared from the AB ring (5) and the E ring fragment (6) utilizing the alkylation-metathesis sequence. The last RCM step (4 → 3) may be a crucial step because the double bond in the E ring might react competitively.

Scheme 2 Reagents and conditions: i) LDA, THF, -78 °C, 71%. ii) 30% H₂O₂, NaHCO₃, THF, 90%. iii) (PCy₃)₂Cl₂Ru=CHPh (7 mol %), CH₂Cl₂ reflux, 2 d, 85% (total). iv) TBSCI, imidazole, DMF, 93%. v) DIBALH, -78 to -50 °C. vi) Ph₃PMeBr, KO'Bu, THF, 53% (2 steps). vii) TBAF, THF, 99%. viii) t-butyldimethylsilylethyl bromoacetate, NaH, 75%. TBSCI=t-butyldimethylsilyl chloride; DMF=N,N-dimethylformamide; DIBALH=diisobutylaluminum hydride; TBAF=tetrabutylammonium fluoride.
Synthesis of the E ring is shown in Scheme 2. Aldol reaction of ester \( (7)^6 \) with aldehyde \( (8)^6 \) followed by treatment with \( \text{H}_2\text{O}_2 \)\(^7 \) gave diene \( (9) \) as an inseparable mixture of diastereomers. RCM reaction of \( (9) \) using Grubbs' catalyst\(^8 \) proceeded smoothly to afford eight-membered cyclic ethers \( (10, 11, \text{ and } 12) \) in 28, 38 and 19\% yields, respectively. Protection of the secondary alcohol of \( 10 \), which has the required stereochemistry, and successive DIBALH reduction and Wittig reaction gave \( 13 \). Deprotection of \( 13 \) followed by alkylation with \( \text{t}-\text{butyl bromoacetate} \) gave the glycolic acid ester derivative \( (6) \).

Although the yield of \( 10 \) is not high, other diastereomers \( (11) \) and \( (12) \) are all useful for the synthesis (Scheme 3). Reduction of the ester \( (11) \), followed by selective protection of the primary alcohol as TBPS ether, and oxidation of the secondary alcohol with Dess-Martin periodinane gave a non-conjugated enone \( (14) \). Removal of the TBPS group of \( 14 \) and stereoselective reduction using NaBH(OAc)\(^9 \) gave diol \( (15) \) as a single isomer. The diol \( (15) \) was converted to \( 13 \) via selective deprotection of the corresponding bis-TBS ether using Guerrero’s method,\(^9 \) and was followed by oxidation of \( 17 \) and subsequent Wittig reaction. The ester \( (12) \) was also converted to \( 13 \) via an enone \( (16) \) which was prepared in an analogous manner. Complete epimerization of \( 16 \) with imidazole\(^6, 11 \) gave the enone \( (14) \) without a migration of the double bond.

Alkylation of the E ring fragment \( (6) \) with the AB ring fragment \( (5)^4 \) gave a 51\% yield of \( 18 \) as an inseparable 6:1 diastereomeric mixture (Scheme 4). Acidic methanolysis of the \( \text{p}-\text{methoxybenzylidene} \) acetal \( (18) \) followed by protection of the resulting 1,3-diol as TIPDS ether, and removal of the MPM group yielded an epimeric mixture of \( 19 \) and \( 20 \), which were easily separated by silica gel column chromatography. Since the stereochemistry at C11 was ambiguous at this stage, we carried out further
transformations using the major product (19). Acid treatment of 19 gave \(\delta\)-lactone (21), which was converted to diene (22) in three steps: i) addition of vinylmagnesium bromide, ii) conversion of the resultant hemiacetal to the methyl acetal, and iii) reduction of the acetal using Et\(_3\)SiH in the presence of HMPA=hexamethylphosphoric triamide; PPTS; pyridinium \(p\)-toluenesulfonate; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone; CSA=10-camphorsulfonic acid; TBAF=tetrabutylammonium fluoride.

Scheme 4 Reagents and conditions: i) PPTS, MeOH, 81%. ii) 1,3-dichlorotetraisopropyldisiloxane, 99%. iii) DDQ, CH\(_2\)Cl\(_2\), 99%. iv) CSA, toluene, 70 °C, 70%. v) vinylmagnesium bromide, Et\(_2\)O, -78 °C, 59%. vi) CH(OMe)\(_3\), CSA, CH\(_2\)Cl\(_2\), 77%. vii) Et\(_3\)SiH, BF\(_3\)Et\(_2\)O, -50−30 °C, 85%. viii) (PCy\(_3\))\(_2\)Cl\(_2\)Ru=CHPh (0.5 mol eq.), CH\(_2\)Cl\(_2\), reflux, 1 d, 43%. ix) TBAF, THF. x) Ac\(_2\)O, py, 82% (2 steps). xi) imidazole, toluene, 110 °C, 85%. xii) vinylmagnesium bromide, Et\(_2\)O, -78 °C, 86%. xiii) CH(OMe)\(_3\), CSA, CH\(_2\)Cl\(_2\), 86%. xiv) Et\(_3\)SiH, BF\(_3\)Et\(_2\)O, -50 °C, 87%. xv) TBAF, THF. xvi) Ac\(_2\)O, py, 82% (2 steps). xvii) (PCy\(_3\))\(_2\)Cl\(_2\)Ru=CHPh (2.8 mol eq.), CDCl\(_3\), 45 °C, 98%.

\(J_{11,12}=6.0\ Hz\)
of BF$_3$·OEt$_2$\textsuperscript{12}. RCM reaction of 22 using Grubbs' catalyst afforded a pentacyclic system (23) without affecting the E ring. However, we found that the stereochemistry at C11 in 23 was not the required one by 1H NMR analysis of the corresponding diacetate (24). Attempts to improve the stereoselectivity in the alkylation reaction between the AB ring and E ring fragments using chiral auxiliary,\textsuperscript{13} or epimerization of the ester (18)\textsuperscript{14} were unsuccessful. However, the lactone (21) underwent epimerization upon treatment with imidazole\textsuperscript{5,11} in toluene at 110 °C to give a separable 1.8:1 mixture of 21 and 25 at a 85% yield. The lactone (25) was converted to diene (26) in a manner analogous to 21. The RCM reaction of 26 using Grubbs' catalyst gave an inseparable mixture of products including the desired pentacyclic ABCDE fragment. The diene (26) was then converted to a less hindered diacetate (4) in two steps at a 82% yield. The RCM reaction of 4 proceeded successfully without interference by the double bond in the E ring to give the ABCDE ring fragment of CTX3C (3) at a 98% yield. The stereochemistry of 3 was unambiguously determined by 1H NMR analysis (NOESY experiment).\textsuperscript{15}

In conclusion, we demonstrated that the alkylation-metathesis strategy is a highly effective method to synthesize the pentacyclic system (3) of 2. Further studies directed toward the total synthesis of 2 are currently in progress in our laboratory.

**REFERENCE AND NOTES**


The ester (7) and aldehyde (8) were readily prepared by the standard procedure from D-glucose (4 steps) and from 1,4-butanediol (2 steps), respectively.


Epimerization of 18 did not proceed by any bases: imidazole, DBU, LDA, KOtBu, or LiNEt2.

Phisical data for 3; [α]D 20 ~54.0° (c 0.28, CHCl3). IR (film) ν 2932, 1749, 1508, 1243, 1092 cm⁻¹. MALDI-TOF MS (alpha) calcd for C₃₃H₄₀O₁₀Na (M+Na⁺) 619.2498, found 619.1809. HRMS (EI, 70 eV) calcd C₃₃H₄₀O₁₀ (M⁺), 596.262, found 596.262. ¹H NMR (500 MHz, CDCl₃) δ 1.43 (1H, q, J=11.3 Hz, H10), 2.05 (3H, s), 2.06 (3H, s), 2.30 (1H, dt, J=11.3, 3.8 Hz, H10'), 2.30-2.35 (1H, m, H4), 2.33 (1H, dd, J=14.0, 9.0 Hz, H17), 2.64 (1H, dd, J=16.1, 7.8,
3.5 Hz, H4’), 2.80 (1H, ddd, J=14.0, 10.0, 3.3 Hz, H17’), 3.06 (1H, t, J=9.0 Hz, H8), 3.11 (1H, td, J=9.0, 3.6 Hz, H9), 3.28 (1H, td, J=9.2, 3.8 Hz, H11), 3.28-3.33 (1H, m, H5), 3.33 (1H, t, J=8.3 Hz, H6), 3.47 (1H, t, J=8.3 Hz, H7), 3.67 (1H, dt, J=9.0, 3.0 Hz, H16), 3.71 (1H, ddd, J=10.0, 6.3, 2.1 Hz, H21), 3.80 (1H, ddd, J=9.2, 4.3, 2.5 Hz, H12), 4.01 (1H, ddd, J=15.4, 6.2, 3.0 Hz, H1), 4.11 (1H, dt, J=9.0, 2.2 Hz, H15), 4.16 (1H, dd, J=10.9, 2.2 Hz, H22), 4.22 (1H, dd, J=10.9, 6.3 Hz, H22’), 4.29 (1H, dd, J=15.4, 5.8 Hz, H1), 4.82 (2H, d, J=11.6 Hz, CH2Ph), 4.87 (2H, d, J=11.6 Hz, CH2Ph), 5.57 (1H, dd, J=11.0, 5.2 Hz, H20), 5.62 (1H, dt, J=12.5, 2.4 Hz, H14), 5.75-5.79 (2H, m, H3 and H19), 5.80 (1H, dt, J=12.5, 2.7 Hz, H13), 5.83-5.89 (2H, m, H2 and H18), 7.30-7.35 (3H, m), 7.38-7.41 (2H, m). 13C NMR (50 MHz, CDCl3) δ 20.91, 21.03, 32.58, 34.64, 36.82, 64.67, 68.37, 70.48, 73.15, 74.81, 75.17, 75.49, 75.69, 75.96, 80.51, 81.76, 81.82, 82.08, 84.39, 87.39, 126.50, 126.73, 127.42, 127.52, 127.73, 128.19, 131.08, 131.34, 132.16, 134.42, 139.15, 168.61, 169.56.