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Convergent synthesis of the IJKLM ring fragment of ciguatoxin CTX3C

Tohru Oishi, Yoko Nagumo, Mitsuru Shoji, Jean-Yves Le Brazidec, Hisatoshi Uehara 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

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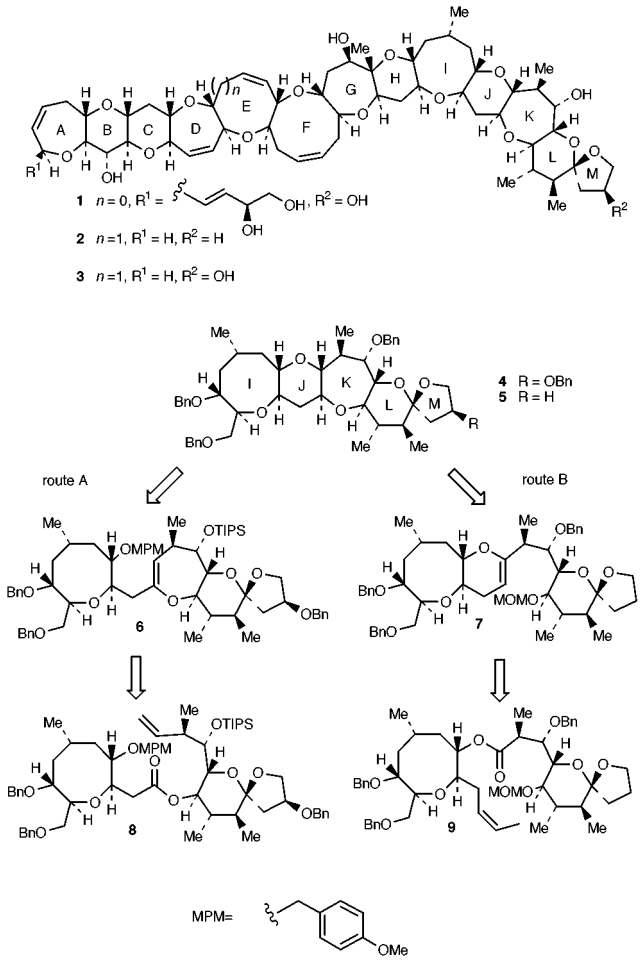
The IJKLM ring fragment of CTX3C, an important member of the ciguatoxin family, was synthesized *via* ring-closing metathesis using the Tebbe reagent and an improved method of reductive hydroxy ketone cyclization.

Ciguatoxin (CTX1B, **1**) and its congeners, CTX3C (**2**) and **3**, are the causative toxins of ciguatera seafood poisoning prevalent in the tropics and subtropics.[1] Although numerous synthetic studies have been reported because of the striking structure and biological activity of these compounds, efficient synthetic methods are still needed for total synthesis. During the course of our synthetic studies directed toward **1**,[2] we recently succeeded in synthesizing the ABCDE ring framework of **1** based on alkylation and ring-closing metathesis (RCM).[3] We describe herein a convergent synthesis of the IJKLM ring fragment of **2**.

Two synthetic routes were envisaged as outlined in Scheme 1. Tebbe reagent mediated transformation[4] of ester **8** (or **9**) into cyclic enol ethers **6** (or **7**), followed by hydroboration–oxidation and reductive hydroxy ketone cyclization protocol[5] provides the IJKLM ring system.

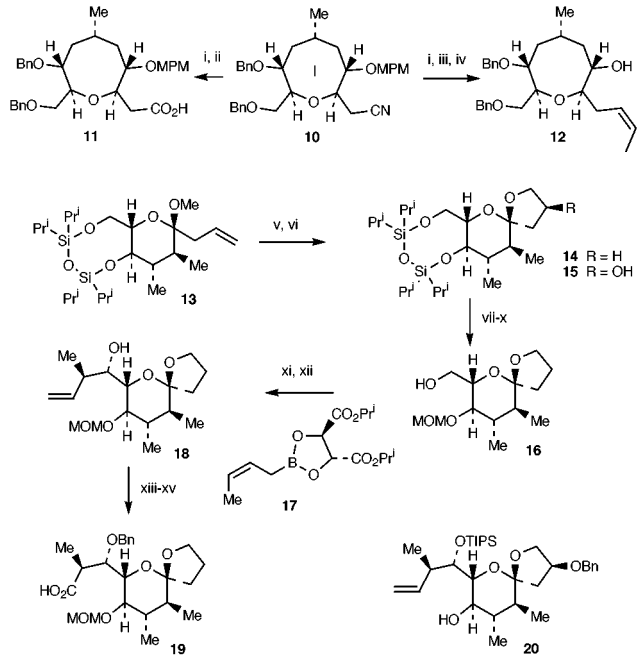


Scheme 1

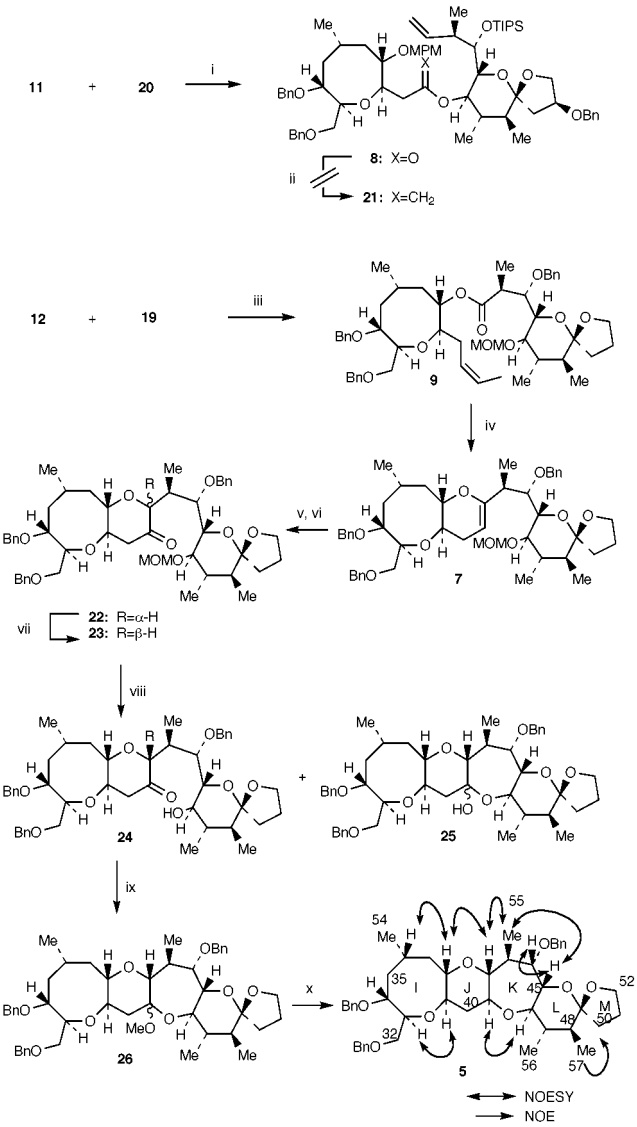
Precursors of the esters **8** and **9** were synthesized as shown in Scheme 2. Carboxylic acid **11** and alcohol **12** were prepared from the I ring moiety **10**[6,7] by the standard procedures. Synthesis of the carboxylic acid **19** corresponding to the LM ring moiety of **2** was initiated with **13**.[8] Hydroboration of **13** using BBN and treatment of the resulting alcohol with CSA gave spiroacetal **14** in 92% yield. Conventional protecting group transformation of **14** yielded alcohol **16**. Dess–Martin periodinane oxidation of **16** followed by asymmetric crotylation using (*R*,*R*,*Z*)-crotylboronate **17**[9] furnished **18** as a single stereoisomer. Protection of the hydroxy group of **18** as a benzyl ether and oxidative cleavage of the double bond gave **19** in 95% yield. Alcohol **20** corresponding to the LM ring moiety of **1** and **3** was synthesized in an analogous manner starting from **15**.[8]

Synthesis of the IJKLM ring fragment was first attempted *via* route A (Scheme 3). Condensation of **11** with **20** using DCC gave **8** in 54% yield, which was treated with the Tebbe reagent in THF at 60 °C. However, olefination of the carbonyl group of **8** did not proceed, and only the initial material **8** was recovered even after 6 h.

The alternative route B was then examined. Coupling of **12** with **19** gave **9** in 74% yield. In contrast to **8**, treatment of **9** with



Scheme 2 *Reagents and conditions*: i, DIBAL-H, CH_2Cl_2, −78 °C; ii, $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, Bu^tOH, H_2O, 41% (2 steps); iii, $Ph_3P^+EtBr^-$, BuLi, THF, −78 °C to room temp., 48% (*Z*:*E* = 4:1, 21% recovery of aldehyde); iv, DDQ, CH_2Cl_2, H_2O, 0 °C, 89%; v, BBN, THF then NaOH, H_2O_2, 88%; vi, CSA, CH_2Cl_2, 92%; vii, TBAF, THF; viii, Bu^tCOCl, Et_3N, CH_2Cl_2, 0 °C to room temp.; ix, MOMCl, Pr^i_2EtN, CH_2Cl_2, 0 to 35 °C; x, $LiAlH_4$, Et_2O, 0 °C to room temp., 76% (4 steps); xi, Dess–Martin periodinane, CH_2Cl_2: xii, **17**, toluene, MS4A, −78 to −60 °C, then $NaBH_4$, −60 to 0 °C, 45% (2 steps, 70% based on recovery of **16**); xiii, NaH, BnBr, THF, DMF, 89%; xiv, OsO_4, NMO, Bu^tOH, H_2O, then $NaIO_4$, pH 7 buffer; xv, $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, Bu^tOH, H_2O, 95% (2 steps).



Scheme 3 *Reagents and conditions*: i, DCC, DMAP, CSA, CH_2Cl_2, 35 °C, 54% (38% recovery of **20**); ii, Tebbe reagent, THF, 60 °C, 95% recovery of **8**; iii, DCC, DMAP, CSA, CH_2Cl_2, 35 °C, 74%; iv, Tebbe reagent, THF, 60 °C, 63%; v, BH_3, THF, 0 °C then NaOH, H_2O_2, 0 °C, 73%; vi, Dess–Martin periodinane, CH_2Cl_2, 100%; vii DBU, CH_2Cl_2, room temp., 1 h; viii, TMSBr, CH_2Cl_2, −78 to −50 °C, **24**: 30%, **25**: 30%; ix, $CH(OMe)_3$, CSA, benzene, 70 to 80 °C, 50%; x, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −73 to 0 °C, 71%.

the Tebbe reagent at 60 °C resulted in the formation of cyclic enol ether **7** in 63% yield *via* methylenation and subsequent RCM.[4] Hydroboration of **7** followed by Dess–Martin periodinane oxidation gave a separable 3:1 mixture of **22** and **23** in 73% yield. The undesired isomer **22** was effectively converted to a 1:1 mixture of **22** and **23** by treatment with DBU in CH_2Cl_2 at room temperature. Removal of the MOM group of **23** with TMSBr gave keto alcohol **24** (30%) and hemiacetal **25** (30%). Direct treatment of the mixture of **24** and **25** with Et_3SiH–TMSOTf[5] gave no products due to reductive hydroxy ketone cyclization. However, reduction of the corresponding methyl acetal[3] **26**, which was prepared from the mixture of **24** and **25**, proceeded stereoselectively using $BF_3{\cdot}OEt_2$ (1.0 equiv.) and Et_3SiH in excess to afford the IJKLM ring fragment **5** in 71% yield without affecting the spiroacetal LM ring moiety.[10] The stereochemistry of **5** was unambiguously determined by ^1H NMR analysis (NOESY and NOE experiments).[11]

In conclusion, we have established a highly convergent route to the IJKLM ring fragment of CTX3C *via* the Tebbe reagent mediated ring-closing metathesis and an improved hydroxy ketone cyclization. Further studies directed toward total synthesis of ciguatoxins are currently in progress in our laboratory.

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10 Excess amount of $BF_3{\cdot}OEt_2$ caused reductive opening of the spiroacetal.

11 *Selected data* for **5**: δ_H (600 MHz, $CDCl_3$) 0.89 (3H, d, *J* 6.3, Me57), 1.02 (3H, d, *J* 6.0, Me56), 1.08 (3H, d, *J* 7.1, Me54), 1.11 (3H, d, *J* 7.7, Me55), 1.41 (1H, br q, *J* 11.7, H40$_{ax}$), 1.50–1.57 (2H, m, H48, H47), 1.63 (1H, br dt, *J* 14.2, 10.2, H37), 1.68 (1H, br ddd, *J* 15.2, 9.5, 6.4, H35), 1.73–1.81 (2H, m, H51, H50), 1.83–1.88 (1H, m, H37), 1.90–1.98 (4H, m, H50, H36, H35, H51), 2.15 (1H, qdd, *J* 7.7, 4.6, 3.5, H43), 2.40 (1H, br dt, *J* 12.0, 4.8, H40$_{eq}$), 2.87 (1H, dd, *J* 9.3, 4.6, H42), 3.06 (1H, br td, *J* 9.6, 3.0, H38), 3.23 (1H, ddd, *J* 11.3, 9.0, 4.4, H39), 3.35 (1H, t, *J* 9.5, H46), 3.41 (1H, br td, *J* 9.2, 2.8, H34), 3.43 (1H, br dd, *J* 3.5, 1.0, H44), 3.44 (1H, dd, *J* 10.0, 6.5, H32), 3.60 (1H, br ddd, *J* 9.3, 6.5, 2.1, H33), 3.64 (1H, dd, *J* 9.5, 1.0, H45), 3.68 (1H, dd, *J* 10.0, 2.1, H32), 3.75 (1H, br q, *J* 7.5, H52), 3.82 (1H, ddd, *J* 11.2, 9.3, 5.0, H41), 3.87 (1H, br td, *J* 7.8, 4.5, H52), 4.32 (1H, d, *J* 11.1, CH_2Ph), 4.55 (2H, s, CH_2Ph), 4.58 (1H, d, *J* 11.1, CH_2Ph), 4.63 (1H, d, *J* 12.2, CH_2Ph), 4.68 (1H, d, *J* 12.2, CH_2Ph), 7.20–7.40 (15H, m, Ph); MALDI-TOF MS calc. for $C_{46}H_{60}O_8Na$ ($M+Na^+$) 763.4186, found 763.4151.

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