

Convergent synthesis of the IJKLM ring fragment of ciguatoxin CTX3C

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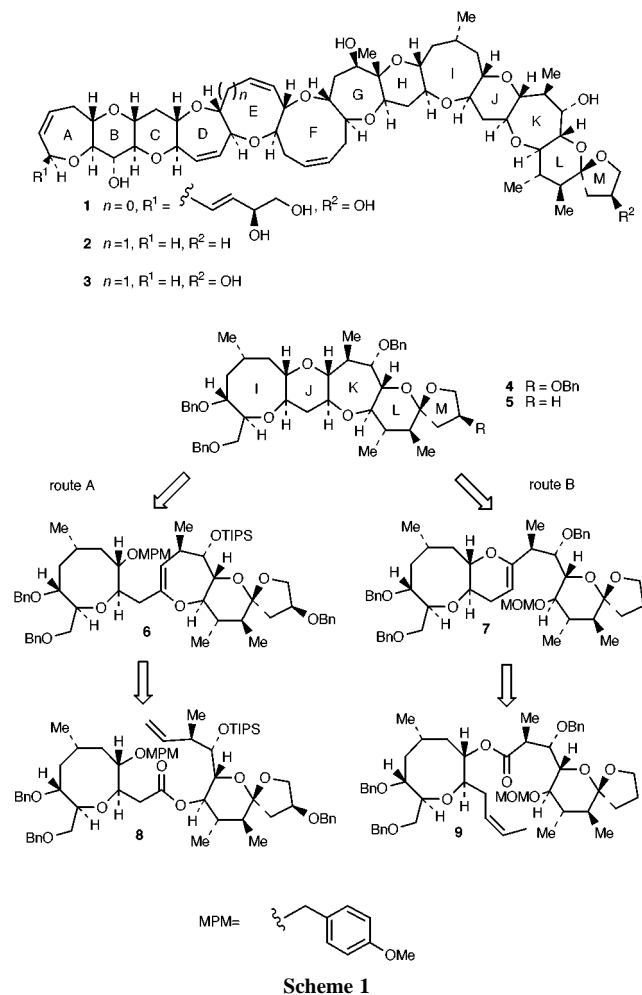
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The IJKLM ring fragment of CTX3C, an important member of the ciguatoxin family, was synthesized via ring-closing metathesis using the Tebbe reagent and an improved method of reductive hydroxy ketone cyclization.

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**.

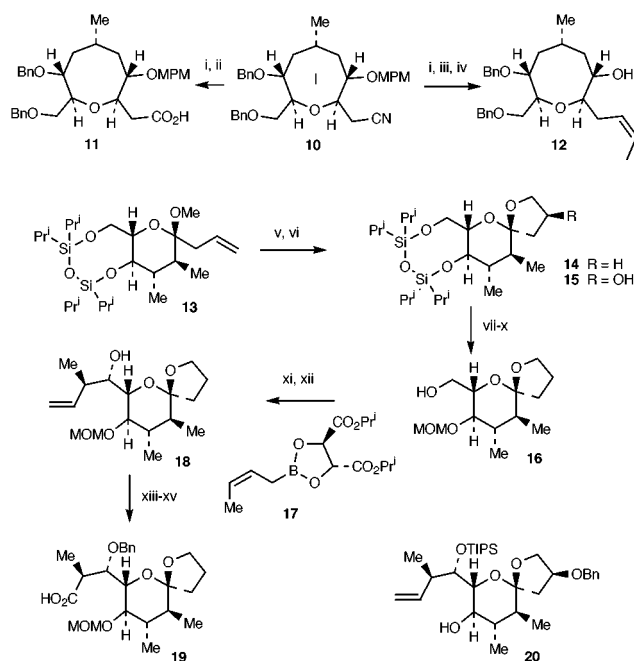
Two synthetic routes were envisaged as outlined in Scheme 1. Tebbe reagent mediated transformation⁴ of ester **8** (or **9**) into cyclic enol ethers **6** (or **7**), followed by hydroboration-oxidation and reductive hydroxy ketone cyclization protocol⁵ provides the IJKLM ring system.



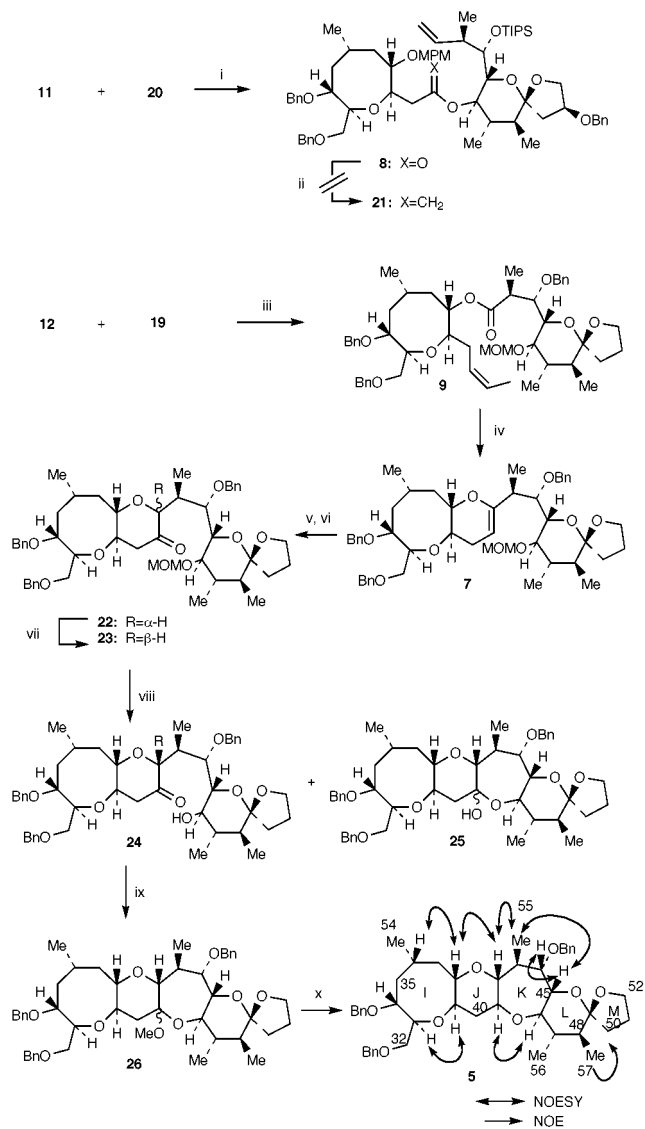
Precursors of the esters **8** and **9** were synthesized as shown in Scheme 2. Carboxylic acid **11** and alcohol **12** were prepared from the I ring moiety **10**^{6,7} by the standard procedures. Synthesis of the carboxylic acid **19** corresponding to the LM ring moiety of **2** was initiated with **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, CH₂Cl₂, –78 °C; ii, NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, Bu^tOH, H₂O, 41% (2 steps); iii, Ph₃P⁺EtBr[–], BuLi, THF, –78 °C to room temp., 48% (*Z*:*E* = 4:1, 21% recovery of aldehyde); iv, DDQ, CH₂Cl₂, H₂O, 0 °C, 89%; v, BBN, THF then NaOH, H₂O₂, 88%; vi, CSA, CH₂Cl₂, 92%; vii, TBAF, THF; viii, Bu^tCOCl, Et₃N, CH₂Cl₂, 0 °C to room temp.; ix, MOMCl, Pr₂EtN, CH₂Cl₂, 0 to 35 °C; x, LiAlH₄, Et₂O, 0 °C to room temp., 76% (4 steps); xi, Dess–Martin periodinane, CH₂Cl₂; xii, **17**, toluene, MS4A, –78 to –60 °C, then NaBH₄, –60 to 0 °C, 45% (2 steps, 70% based on recovery of **16**); xiii, NaH, BnBr, THF, DMF, 89%; xiv, OsO₄, NMO, Bu^tOH, H₂O, then NaIO₄, pH 7 buffer; xv, NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, Bu^tOH, H₂O, 95% (2 steps).



Scheme 3 Reagents and conditions: i, DCC, DMAP, CSA, CH₂Cl₂, 35 °C, 54% (38% recovery of **20**); ii, Tebbe reagent, THF, 60 °C, 95% recovery of **8**; iii, DCC, DMAP, CSA, CH₂Cl₂, 35 °C, 74%; iv, Tebbe reagent, THF, 60 °C, 63%; v, BH₃, THF, 0 °C then NaOH, H₂O₂, 0 °C, 73%; vi, Dess–Martin periodinane, CH₂Cl₂, 100%; vii DBU, CH₂Cl₂, room temp., 1 h; viii, TMSBr, CH₂Cl₂, –78 to –50 °C, **24**: 30%, **25**: 30%; ix, CH(OMe)₃, CSA, benzene, 70 to 80 °C, 50%; x, Et₃SiH, BF₃·OEt₂, CH₂Cl₂, –73 to 0 °C, 71%.

the Tebbe reagent at 60 °C resulted in the formation of cyclic enol ether **7** in 63% yield *via* methylation 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 CH₂Cl₂ 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 Et₃SiH–TMSOTf⁵ gave no products due to reductive hydroxy ketone cyclization. However, reduction of the corresponding methyl acetal³ **26**, which was prepared from the mixture of **24** and **25**, proceeded stereoselectively using BF₃·OEt₂ (1.0 equiv.) and Et₃SiH 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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- Excess amount of BF₃·OEt₂ caused reductive opening of the spiroacetal.
- Selected data for **5**: δ_H (600 MHz, CDCl₃) 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, CH₂Ph), 4.55 (2H, s, CH₂Ph), 4.58 (1H, d, J 11.1, CH₂Ph), 4.63 (1H, d, J 12.2, CH₂Ph), 4.68 (1H, d, J 12.2, CH₂Ph), 7.20–7.40 (15H, m, Ph); MALDI-TOF MS calc. for C₄₆H₆₀O₈Na (M+Na⁺) 763.4186, found 763.4151.

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