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Practical entry into the HIJKLM ring segment of ciguatoxin CTX3C

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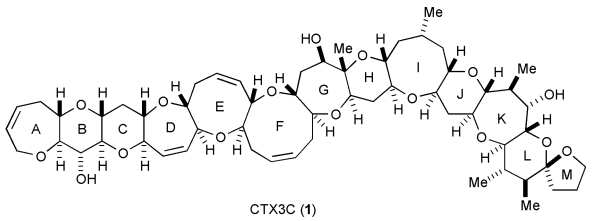
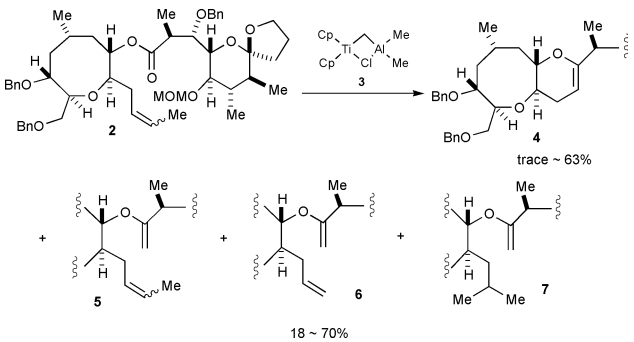
The HIJKLM ring segment (27) of the right half portion of ciguatoxin CTX3C (1) has been synthesized using a ring-closing reaction mediated by a low-valent titanium reagent.

During the course of our synthetic studies directed toward ciguatoxins,[1,2] we have recently reported the convergent synthesis of the ABCDE[3] and IJKLM[4] ring fragment of **1**, based



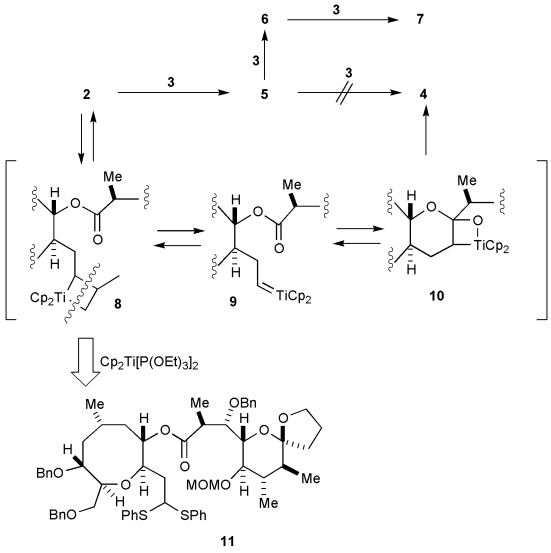
upon an alkylation-ring closing metathesis (RCM) strategy[5,6] and a Tebbe reagent (**3**)[7] mediated ester olefination-ring closing metathesis sequence,[8] respectively. Occasionally, however, the key transformation of **2** into **4** in the latter sequence turned out to be non-reproducible. The yield of **4** fluctuated between trace amount to 63% and concomitant formation of an inseparable mixture of enol ethers, **5**, **6**, and **7** tended to occur (Scheme 1). Unfortunately, irrespective of extensive investigation, secure conditions to yield **4** uniformly could not be found. At low conversions **5** sometimes predominated, while **6** and then **7** gradually increased as the reaction time was extended. Since the intermediacy of the diene **5** in the formation of **4** was conceivable,[8] mixtures which contained **5** as the major product were treated with **3** or the Schrock catalyst, 2,6-(^{i}Pr)$_2$C$_6$H$_3$-N=Mo[OC(CF$_3$)$_2$Me]$_2$=CHCMe$_2$Ph.[9–11] However, in remarkable contrast to literature precedent, **4** was not produced in appreciable amounts; instead **6** and **7** increased.[8] Steric hindrance around the diene system of **5** is likely to account for this unexpected failure of converting **5** into **4**. Mechanistically, there should exist an alternative pathway (**2** ⇌ **8** ⇌ **9** ⇌ **10** ⇌ **4**) to provide **4**, in which the ester carbonyl group reacts with an



Scheme 1

internal carbenoid species such as **9** (Scheme 2). Thus, we reasoned that exclusive formation of **9** would improve the yield of **4** and that **9** could be prepared from the phenylthioacetal **11** using the low-valent titanium complex Cp$_2$Ti[P(OEt)$_3$]$_2$ recently developed by Takeda.[12]

The dithioacetal **11** was synthesized as shown in Scheme 3. Although we had synthesized the I-ring moiety of **1** based on a ring-expansion strategy,[13] we developed an alternative route applicable to large-scale synthesis. Aldol reaction of glycolate **12**[14] with acrolein gave diene **13** as an epimeric mixture of alcohols (47%), which was separated from other diastereomers by flash column chromatography (40% combined yield). RCM reaction of **13** using Grubbs catalyst, (PCy$_3$)$_2$Cl$_2$Ru=CHPh,[15] proceeded smoothly to give the eight-membered cyclic ether **14** (60%). Reduction of the ester **14** followed by selective protection of the resulting primary alcohol as TBDPS ether, and Swern oxidation of the secondary alcohol gave the enone **15** (3 steps, 68%). Stereoselective introduction of the secondary methyl group was successfully achieved by conjugate addition with Me$_2$Cu(CN)Li$_2$ to afford **16** in 74% yield. Removal of the TBDPS group of **16** using TBAF in the presence of AcOH, and reduction of the resulting hydroxy ketone with NaBH(OAc)$_3$ gave the diol **17** as a single isomer (92%).[16] Bis-benzylation, acetal hydrolysis followed by a two step cyanation sequence yielded the nitrile **18** (46% overall yield). Protection, DIBAL-H reduction and thioacetalization gave the dithioacetal **19** (3 steps, 73%), which was condensed with the carboxylic acid **20**[4] to afford **11** (58%). Ring-closing reaction of **11** was then examined. A THF solution of **11** was added to excess Takeda reagent (Cp$_2$Ti[P(OEt)$_3$]$_2$)[12] at rt and then refluxed under an argon atmosphere for 1 h. Using this protocol, the cyclic enol ether was formed reproducibly in 52–67% yield even on a one or two gram scale, while reduction and elimination products of the phenylthio group, **21** and **22**, respectively, were only produced in minor amount, *ca.* 10% combined yield.



Scheme 2

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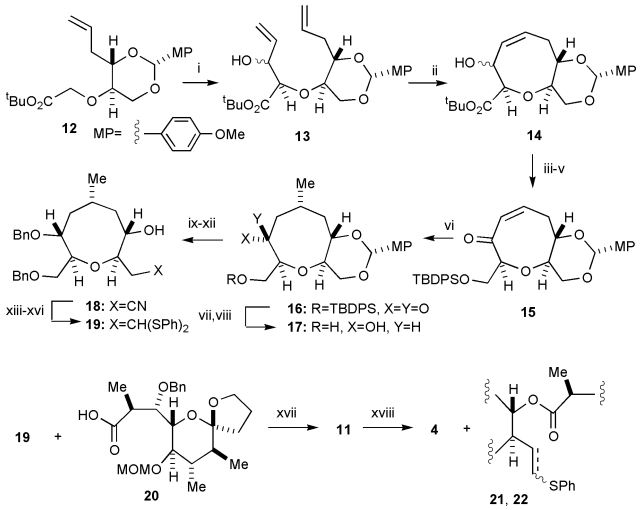
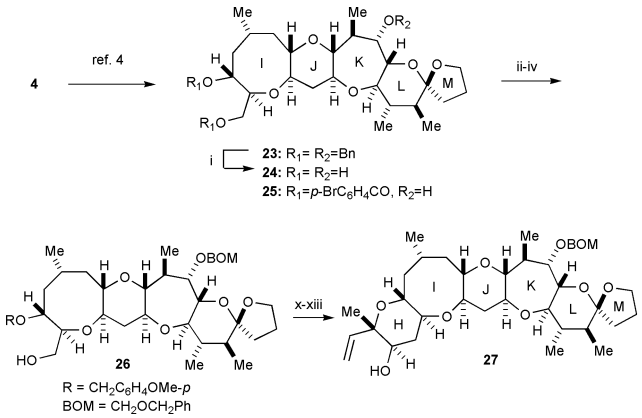


Scheme 3 *Reagents and conditions*: i, LDA, acrolein, THF, −78 °C, 10 min, separation, 47%; ii, $(PCy_3)_2Cl_2Ru$=CHPh (10 mol%), CH_2Cl_2 (0.01 M), reflux, 24 h, 60%; iii, LAlH, THF, 0 °C to rt, 5 h, 98%; iv, TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 16 h, 88%; v, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 30 min, 79%; vi, $Me_2Cu(CN)Li_2$, Et_2O, −78 °C, 30 min, 74%; vii, TBAF, AcOH, THF, rt, 5 h, 95%; viii, $NaBH(OAc)_3$, AcOH, CH_3CN, −20 °C, 2 h, 97%; ix, BnBr, NaH, THF, DMF, 0 °C to rt, 20 h; x, $TsOH·H_2O$, MeOH, H_2O, rt, 1 d, 68%; xi, I_2, PPh_3, imidazole, THF, 0 °C to rt, 1 d, 87%; xii, NaCN, DMSO, 40 °C, 2 d, 78%; xiii, TESOTf, 2,6-lutidine, CH_2Cl_2, −30 to −20 °C, 15 min, quant.; xiv, DIBAL-H, CH_2Cl_2, −70 to −60 °C, 1 h; xv, PhSSPh, Bu_3P, benzene, rt, 12 h, 73% (2 steps); xvi, TBAF, THF, rt, 3 h, 95%; xvii, EDC·HCl, DMAP, CH_2Cl_2, rt, 12 h, 58%; xviii, $Cp_2Ti[P(OEt)_3]_2$ (3 or 4 eq.), THF, reflux, 1 h, **4**: 52–67%, **21**, **22**: ~10%.



Scheme 4 *Reagents and conditions*: i, H_2, $Pd(OH)_2$/C, EtOAc, MeOH, rt, 1 d; ii, *p*-$MeOC_6H_4CH(OMe)_2$, CSA, CH_2Cl_2, rt, 30 min, 89% (2 steps); iii, BOMCl, $^iPr_2NEt$, $(CH_2Cl)_2$, 40 °C, 12 h, 88%; iv, DIBAL-H, CH_2Cl_2, −80 to −30 °C, 2 h, 85%; v, MsCl, Et_3N, $(CH_2Cl)_2$, 0 °C, 40 min; vi, NaCN, 18-crown-6, DMF, 50 °C, 3 d, 98% (2 steps); vii, DIBAL-H, CH_2Cl_2, −80 to −70 °C, 30 min; viii, Ph_3P=C(Me)CO_2Et, toluene, rt, 3 h, 84% (2 steps); ix, DIBAL-H, CH_2Cl_2, −70 °C, 20 min, 94%; x, D-(−)-DET, $Ti(O^iPr)_4$, Bu^tOOH, MS4A, CH_2Cl_2, −50 to −30 °C, 2 h, 80%; xi, SO_3·Py, Et_3N, CH_2Cl_2, 0 °C to rt, 2 h; xii, $Ph_3P^+CH_3Br^-$, NaHMDS, THF, 0 °C, 20 min, 96% (2 steps); xiii, DDQ, H_2O, CH_2Cl_2, rt, 2 h, 82%.

The enol ether **4** was converted to the IJKLM-ring fragment **23** according to our previously reported procedure (Scheme 4).[4] The stereochemistry of **23** was unambiguously determined by X-ray crystallography of the corresponding bis-*p*-bromobenzoate **25** (Fig. 1).[17] Furthermore, the H-ring moiety was successfully constructed in **23** in a similar manner to our previously established route[18] in 32% overall yield utilizing acid catalyzed vinylepoxide–alcohol cyclization methodology.[19]

In short, a practical synthetic route to the HIJKLM ring fragment **27** has been established. Further studies directed towards the total synthesis of ciguatoxin CTX3C (**1**) are currently in progress in our laboratory.

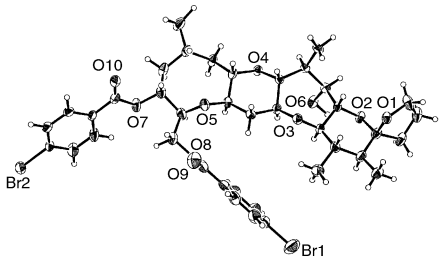


Fig. 1 ORTEP drawing of bis-*p*-bromobenzoate **25**.

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17 *Crystal data*: $C_{39}H_{48}O_{10}Br_2$, M = 836.61, orthorhombic, space group $P2_12_12_1$, Dc = 1.440 g cm^{-3}, Z = 4, a = 5.5284(3), b = 25.006(2), c = 27.913(2) Å, V = 3858.7(4) Å^3, F(000) = 1728, μ(Mo-Kα) = 21,63 cm^{-1}, R = 0.053, Rw = 0.152. CCDC 154471. See http://www.rsc.org/suppdata/cc/b0/b009506k/ for crystallographic files in .cif format.

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