

# Practical entry into the HIJKLM ring segment of ciguatoxin CTX3C

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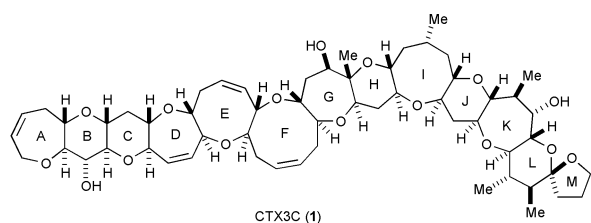
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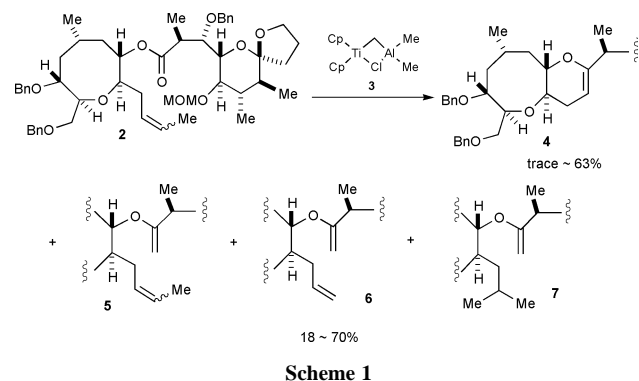
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The HIJKLM ring segment (27) of the right half portion of ciguatoxin CTX3C (1) has been synthesized using a ring-closing reaction mediated by a low-valent titanium reagent.

During the course of our synthetic studies directed toward ciguatoxins,<sup>1,2</sup> we have recently reported the convergent synthesis of the ABCDE<sup>3</sup> and IJKLM<sup>4</sup> ring fragment of 1, based

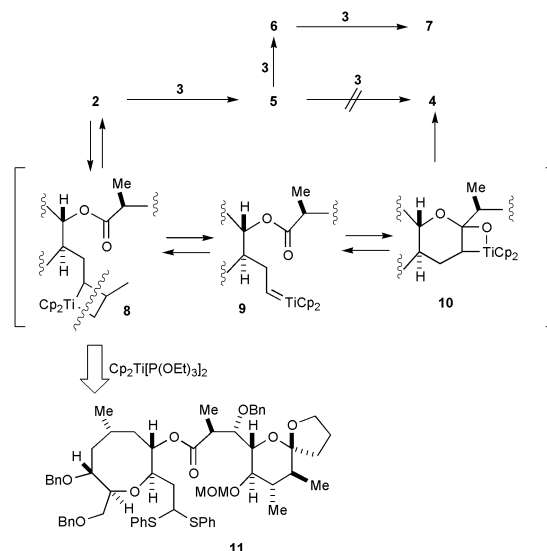


upon an alkylation-ring closing metathesis (RCM) strategy<sup>5,6</sup> and a Tebbe reagent (3)<sup>7</sup> mediated ester olefination-ring closing metathesis sequence,<sup>8</sup> respectively. Occasionally, however, the key transformation of 2 into 4 in the latter sequence turned out to be non-reproducible. 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,<sup>8</sup> mixtures which contained 5 as the major product were treated with 3 or the Schrock catalyst, 2,6-(*i*Pr)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-N=Mo[OC(CF<sub>3</sub>)<sub>2</sub>Me]<sub>2</sub>=CHCMe<sub>2</sub>Ph.<sup>9-11</sup> However, in remarkable contrast to literature precedent, 4 was not produced in appreciable amounts; instead 6 and 7 increased.<sup>8</sup> 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

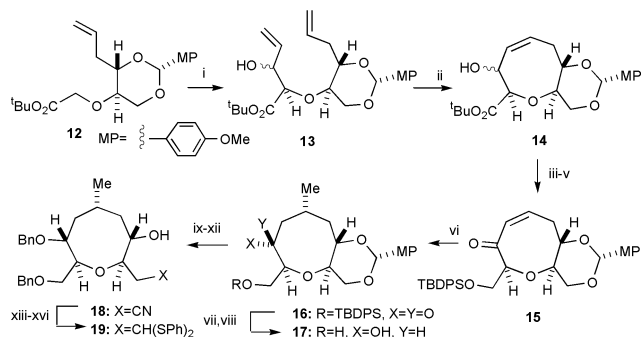


internal carbenoid species such as 9 (Scheme 2). Thus, we reasoned that exclusive formation of 9 would improve the yield of 4 and that 9 could be prepared from the phenylthioacetal 11 using the low-valent titanium complex Cp<sub>2</sub>Ti[P(OEt)<sub>3</sub>]<sub>2</sub> recently developed by Takeda.<sup>12</sup>

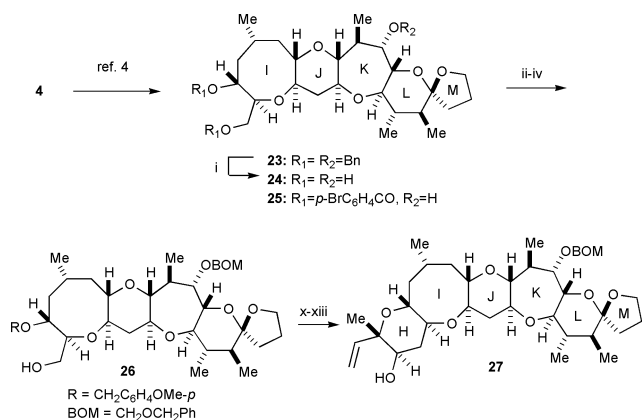
The dithioacetal 11 was synthesized as shown in Scheme 3. Although we had synthesized the I-ring moiety of 1 based on a ring-expansion strategy,<sup>13</sup> we developed an alternative route applicable to large-scale synthesis. Aldol reaction of glycolate 12<sup>14</sup> with acrolein gave diene 13 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<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>Ru=CHPh,<sup>15</sup> 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<sub>2</sub>Cu(CN)Li<sub>2</sub> 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)<sub>3</sub> gave the diol 17 as a single isomer (92%).<sup>16</sup> 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<sup>4</sup> to afford 11 (58%). Ring-closing reaction of 11 was then examined. A THF solution of 11 was added to excess Takeda reagent (Cp<sub>2</sub>Ti[P(OEt)<sub>3</sub>]<sub>2</sub>)<sup>12</sup> 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.



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**Scheme 3 Reagents and conditions:** i, LDA, acrolein, THF,  $-78^{\circ}\text{C}$ , 10 min, separation, 47%; ii,  $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$  (10 mol%),  $\text{CH}_2\text{Cl}_2$  (0.01 M), reflux, 24 h, 60%; iii, LAH, THF,  $0^{\circ}\text{C}$  to rt, 5 h, 98%; iv, TBDPSCl,  $\text{Et}_3\text{N}$ , DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 16 h, 88%; v,  $(\text{COCl})_2$ , DMSO,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-60^{\circ}\text{C}$ , 30 min, 79%; vi,  $\text{Me}_2\text{Cu}(\text{CN})\text{Li}_2$ ,  $\text{Et}_2\text{O}$ ,  $-78^{\circ}\text{C}$ , 30 min, 74%; vii, TBAF, AcOH, THF, rt, 5 h, 95%; viii,  $\text{NaBH}(\text{OAc})_3$ , AcOH,  $\text{CH}_3\text{CN}$ ,  $-20^{\circ}\text{C}$ , 2 h, 97%; ix, BnBr, NaH, THF, DMF,  $0^{\circ}\text{C}$  to rt, 20 h; x, TsOH-H<sub>2</sub>O, MeOH, H<sub>2</sub>O, rt, 1 d, 68%; xi, I<sub>2</sub>, PPh<sub>3</sub>, imidazole, THF,  $0^{\circ}\text{C}$  to rt, 1 d, 87%; xii, NaCN, DMSO,  $40^{\circ}\text{C}$ , 2 d, 78%; xiii, TESOTf, 2,6-lutidine,  $\text{CH}_2\text{Cl}_2$ ,  $-30$  to  $-20^{\circ}\text{C}$ , 15 min, quant.; xiv, DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-70$  to  $-60^{\circ}\text{C}$ , 1 h; xv, PhSSPh, Bu<sub>3</sub>P, benzene, rt, 12 h, 73% (2 steps); xvi, TBAF, THF, rt, 3 h, 95%; xvii, EDC-HCl, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt, 12 h, 58%; xviii,  $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$  (3 or 4 eq.), THF, reflux, 1 h, **4**: 52–67%, **21**, **22**: ~10%.



**Scheme 4 Reagents and conditions:** i, H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, EtOAc, MeOH, rt, 1 d; ii, *p*-MeOC<sub>6</sub>H<sub>4</sub>CH(OMe)<sub>2</sub>, CSA,  $\text{CH}_2\text{Cl}_2$ , rt, 30 min, 89% (2 steps); iii, BOMCl,  $\text{Pr}_2\text{NEt}$ ,  $(\text{CH}_2\text{Cl})_2$ ,  $40^{\circ}\text{C}$ , 12 h, 88%; iv, DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-80$  to  $-30^{\circ}\text{C}$ , 2 h, 85%; v, MsCl,  $\text{Et}_3\text{N}$ ,  $(\text{CH}_2\text{Cl})_2$ ,  $0^{\circ}\text{C}$ , 40 min; vi, NaCN, 18-crown-6, DMF,  $50^{\circ}\text{C}$ , 3 d, 98% (2 steps); vii, DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-80$  to  $-70^{\circ}\text{C}$ , 30 min; viii,  $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$ , toluene, rt, 3 h, 84% (2 steps); ix, DIBAL-H,  $\text{CH}_2\text{Cl}_2$ ,  $-70^{\circ}\text{C}$ , 20 min, 94%; x, D-(−)-DET, Ti(O<sup>i</sup>Pr)<sub>4</sub>, Bu<sup>t</sup>OOH, MS4A,  $\text{CH}_2\text{Cl}_2$ ,  $-50$  to  $-30^{\circ}\text{C}$ , 2 h, 80%; xi, SO<sub>3</sub>-Py,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $0^{\circ}\text{C}$  to rt, 2 h; xii,  $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$ , NaHMDS, THF,  $0^{\circ}\text{C}$ , 20 min, 96% (2 steps); xiii, DDC, H<sub>2</sub>O,  $\text{CH}_2\text{Cl}_2$ , rt, 2 h, 82%.

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

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.

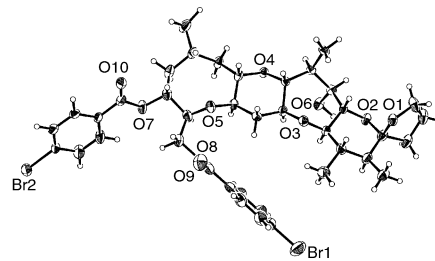


Fig. 1 ORTEP drawing of bis-*p*-bromobenzoate **25**.

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