

Bidirectional Synthesis of the IJK Fragment of Ciguatoxin CTX3C by Sequential Double Ring-Closing Metathesis and Tsuji–Trost Allylation

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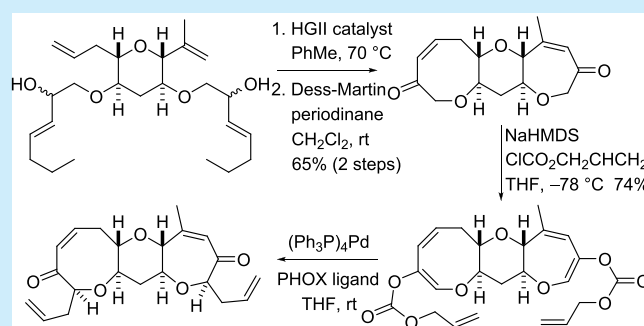


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ABSTRACT: A novel four-step bidirectional strategy has been used to synthesize the IJK fragment of the marine polyether natural product CTX3C from a simple monocyclic precursor in a concise and efficient manner. The four-step bidirectional sequence involves ring-closing metathesis, alcohol oxidation, enol carbonate formation, and palladium-mediated Tsuji–Trost allylation.



The fused polyether natural product CTX3C is one of more than a dozen ciguatoxins to have been isolated from algae or fish collected in tropical or subtropical regions of the Pacific Ocean or Indian Ocean, or from samples collected in the Caribbean Sea (Figure 1).^{1,2} The ciguatoxins are extremely potent neurotoxins, and in common with many other large fused polyether natural products of marine origin (e.g., the brevetoxins), they disrupt the transmission of nerve signals by binding at site 5 on voltage-sensitive sodium channels.³ Human exposure to the ciguatoxins by ingestion of contaminated fish or seafood results in a condition known as ciguatera in which sufferers exhibit severe neurological, gastrointestinal, and cardiovascular problems; fatalities, although rare, have been recorded.⁴

CTX3C was first isolated from a culture of the marine dinoflagellate *Gambierdiscus toxicus* and characterized by Yasumoto and co-workers in 1993 (Figure 1).¹ The molecular structure of CTX3C comprises 13 fused cyclic ethers, with ring sizes that vary from five to nine, and is typical of the ciguatoxin family. The size, complexity, and number of medium-sized cyclic ethers embedded in its structure make CTX3C an extremely challenging yet alluring target for total synthesis. Although several groups have synthesized major portions of the natural product over the past two decades,⁵ the crowning achievements in this area are undoubtedly the impressive and elegant total syntheses of CTX3C and 51-hydroxy-CTX3C, completed by Hirma and co-workers,⁶ and the more recent total synthesis of CXT1B, completed by Isobe and Hamajima.⁷

As part of our general program concerning the development of new reactions and strategies for the rapid and efficient synthesis of fused polycyclic ether arrays, we have explored the

use of iterative and bidirectional approaches to synthesize large fragments of the gambieric acids and CTX3C.^{8,9} In our previous work concerning the synthesis of CTX3C, the A–E fragment of CTX3C was assembled by a route in which ring-closing metathesis (RCM) reactions were used to construct four of the five rings including the medium-sized A, D, and E rings.⁹ We now present a novel approach to the synthesis of the IJK fragment of CTX3C in which a four-step sequence is performed bidirectionally to assemble this key tricyclic fragment from a simple monocyclic precursor.

Our retrosynthetic analysis of CTX3C is shown in Figure 1. Disconnection through the rings G and H implies that the fused 13-ring framework will be constructed by coupling of an A–F fragment i with an I–M fragment ii followed by formation of rings G and H. Further disconnection of the I–M fragment ii through the LM spiroacetal then reveals the tricyclic fragment iii and removal of the methyl substituent from ring I, and the hydroxyl group from ring K suggests bis-enone iv as a key intermediate. Removal of the side chains and scission of both enones then reveals the J-ring fragment v.

Implicit in our retrosynthetic analysis of the I–M fragment is formation of rings I and K by RCM and installation of the side chains of both rings by Tsuji–Trost allylation,¹⁰ a reaction that we have already demonstrated as being highly effective for the

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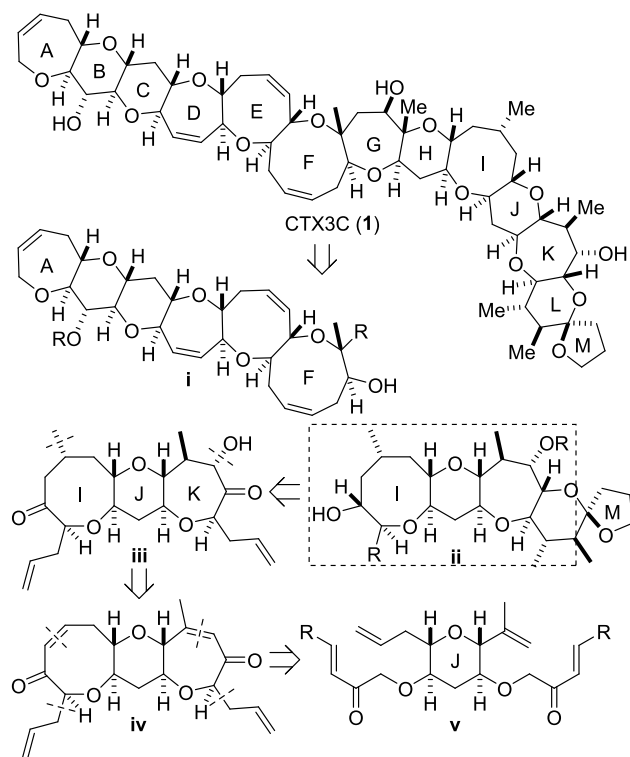


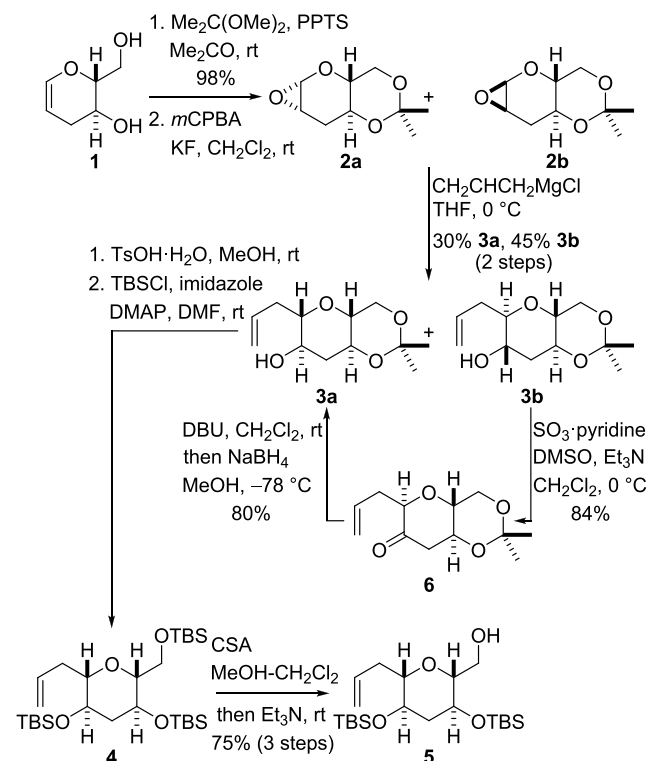
Figure 1. Disconnection of ciguatoxin CTX-3C (1) to reveal the IJK fragment iv and further disconnection to I-ring fragment v.

stereoselective functionalization of seven- and eight-membered cyclic ethers.¹¹ We chose to pursue a highly ambitious approach in which RCM, Tsuji–Trost allylation, and the intermediate reactions would be performed bidirectionally in order to minimize the number of steps.

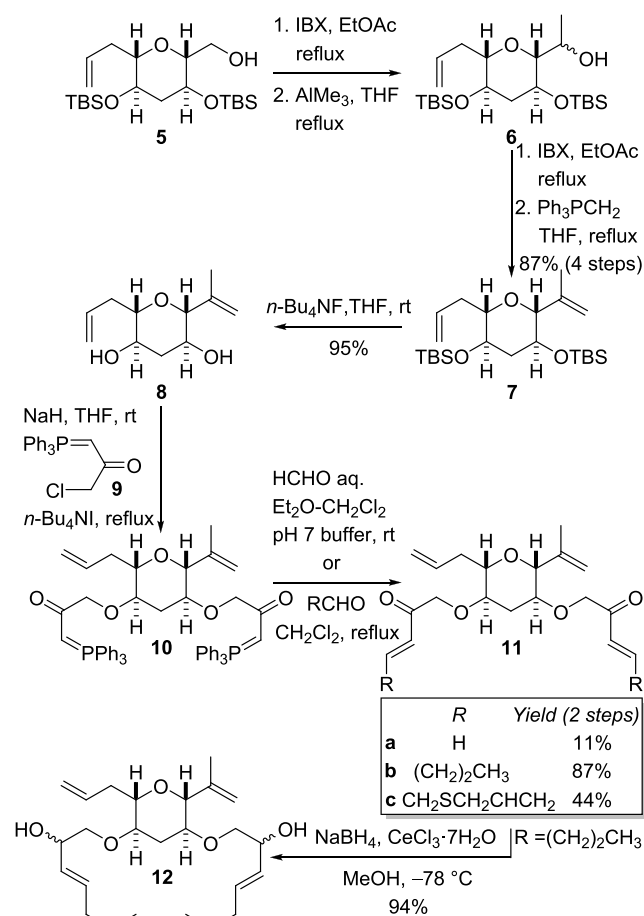
The synthesis of the precursor required for the bidirectional sequence commenced with the enantiomerically pure enol ether **1**, which was prepared in two steps from commercially available tri-*O*-acetyl-D-glucal (Scheme 1).^{8b} The 1,3-diol was converted into an acetonide and the enol ether was epoxidized thereafter by treatment with *m*-CPBA in the presence of KF according to a procedure used by Chiappe and co-workers for the epoxidation of structurally related glycals.¹² This reaction was chosen because it was more amenable to scale-up than the more widely used DMDO epoxidation procedure, and the unstable epoxides could be isolated more rapidly.¹³ The resulting mixture of diastereomeric glycal epoxides **2a** and **2b** was treated directly with allylmagnesium chloride to produce the diastereomeric alcohols **3a** and **3b** in a combined yield of 75% over two steps. The alcohol **3b** was recovered and converted into the required diastereomer **3a** by sequential oxidation, epimerization, and reduction. The alcohol **3a** was then converted into the corresponding triol by acid-mediated cleavage of the acetonide. Persilylation was performed by treatment of the triol with 4 equiv of *tert*-butyldimethylsilyl chloride, an excess of imidazole, and a substoichiometric amount of DMAP to deliver the tetrahydropyran **4**. Selective monodeprotection to give the primary alcohol **5** was accomplished by treatment of the intermediate **4** with camphorsulfonic acid.¹⁴

The precursors (**11a–c** and **12**) required for exploration of the bidirectional RCM reaction were prepared from the alcohol **5** as shown in Scheme 2. The primary alcohol **5** was converted into a diastereomeric mixture of the secondary

Scheme 1. Synthesis of the Alcohol **5a** from the Glucal **1**



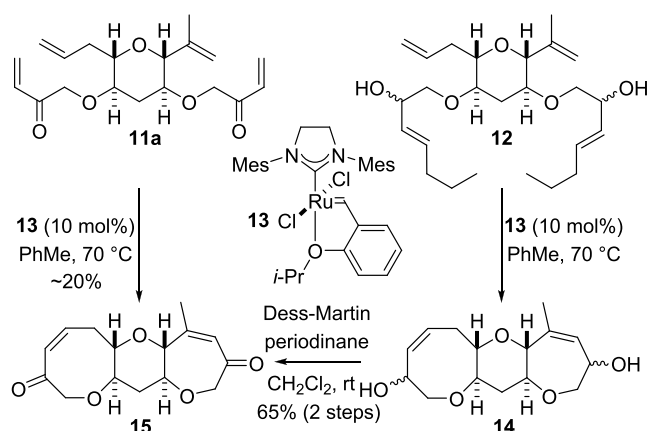
Scheme 2. Preparation of the Bidirectional RCM Precursors **11a–c** and **12** from the Alcohol **5**



alcohol **6** by oxidation and addition of trimethylaluminum to the resulting aldehyde.¹⁵ Oxidation of the alcohol to give the corresponding ketone was followed by Wittig methylation to produce the diene **7**. Cleavage of both silyl ethers was accomplished by treatment of the diene **7** with tetra-*n*-butylammonium fluoride. The resulting diol **8** was then subjected to double alkylation with α -chloroketophosphorane **9**.^{11,16} The resulting *bis*-ylide **10** was then reacted with formaldehyde, butanal, or 2-(2-propen-1-ylthio)acetaldehyde¹⁷ to give the RCM substrates **11a–c** with variable yields. Subsequent reduction of the *bis*-enone **11b** under Luche conditions delivered the diol **12**, the fourth RCM substrate required for exploration of the bidirectional strategy, as a complex mixture comprising all four diastereomers.

The proposed bidirectional RCM reaction to form rings I and K simultaneously was challenging because it involves the formation of two medium-sized rings, one of the reacting alkenes is 1,1-disubstituted, and there are potential reactivity issues when enones are used as substrates in RCM reactions.¹⁸ Bidirectional RCM reactions of all four substrates (**11a–c** and **12**) were explored; the Hoveyda–Grubbs second generation complex (**13**) was used because we had found it to be the optimum catalyst for the cyclization of simpler substrates to produce medium-sized cyclic ethers (Scheme 3).¹¹ The RCM

Scheme 3. Bidirectional RCM Reactions of the Substrates 11a and 12

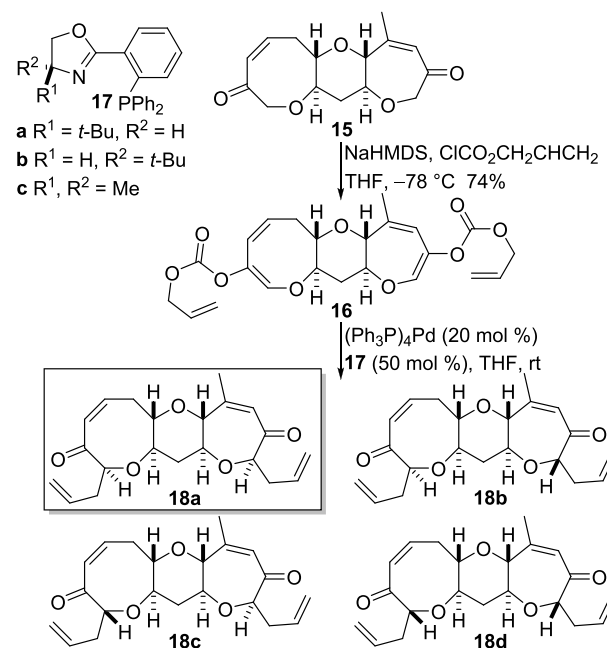


reaction of substrate **11a** was low-yielding (yield ~20%) as was the reaction used to prepare the substrate, and so the sequence was not viable. Cyclization of substrate **11b** by double RCM was performed with the expectation that the propyl groups would direct intermolecular formation of the intermediate ruthenium carbenes to the terminal alkenes instead of the enones,^{18,19} thereby avoiding the generation of potentially less reactive enone-derived alkylidenes. Unfortunately, reaction of the substrate **11b** with the complex **13** did not produce the required tricyclic product **15**. The possibility of performing relay RCM in order to favor alkylidene formation at the enone sites was also explored. The substrate **11c**, which incorporates an allylic sulfide, was chosen because allylic sulfides are known to be particularly reactive substrates in RCM reactions mediated by the Hoveyda–Grubbs second generation complex (**13**).²⁰ However, attempts to perform bidirectional relay RCM of the substrate **11c** were thwarted by degradation of this substrate instead of formation of the required tricyclic product **15**.²¹ Finally, we explored the cyclization of the diol **12** with the expectation that the allylic alcohols would be more reactive

RCM partners than the corresponding enones (Scheme 3).¹¹ This approach was highly successful, and the diastereomeric mixture of the tetraene **12** underwent RCM to give a diastereomeric mixture of the tricyclic diol **14**.²² Immediate oxidation of the diastereomeric mixture of diols produced the *bis*-enone **15** in 65% yield over two steps. The RCM reaction was sensitive to temperature, concentration, and catalyst loading.²³ Reduction of either the reaction temperature or catalyst loading resulted in a lower yield of the diol **14** and the isolation of significant amounts of the bicyclic product in which the eight-membered ring had formed, but the seven-membered ring had not.

The final sequence required to complete the IJK fragment was conversion of each carbonyl group of the *bis*-enone **15** into an enol carbonate followed by a double Tsuji–Trost reaction to install the allyl side chains simultaneously (Scheme 4).^{10,11}

Scheme 4. Bidirectional Functionalization of the IJK Ring System



The tricyclic *bis*-enone **15** was converted into the precursor (**16**) required for the allylation reaction by treatment with sodium bis(trimethylsilyl)amide and *in situ* trapping of the resulting enolates with allyl chloroformate at low temperature.²⁴ The resulting *bis*-carbonate **16** was then subjected to Tsuji–Trost allylation reactions mediated by palladium complexes of the PHOX ligands **17a–c** (Scheme 4, Table 1).¹¹ The reaction mediated by the achiral dimethyl-PHOX ligand **17c** delivered a mixture of the diastereomers **18a–c** (entry 1, Table 1).²⁵ The product ratio suggests that the level of substrate stereocontrol for allylation in the eight-membered ring is just 54:46 (favoring *S* configuration at the newly created stereogenic center), an outcome that is consistent with the low level of stereocontrol obtained when a similar fused eight-membered cyclic ether was allylated under these reaction conditions. In the case of the seven-membered ring, data indicate that substrate stereocontrol is approximately 91:9 (favoring *R* configuration at the newly created stereogenic center), which is significantly higher than the level of stereocontrol obtained when the allylation reaction was

Table 1. Double Tsuji–Trost Allylation Reactions of *bis*-Carbonate **16 Catalyzed by Palladium Complexes of Ligands **17a–c****

Entry	Ligand	Product ratio ^a				Yield ^b
		18a	18b	18c	18d	
1	17c	45	9	46	–	–
2	17a	40	49	11	–	75%
3	17b	37	–	63	–	70%
4	(±)-17a/b	42	7	51	–	–

^aRatio of diastereomeric products **18a–d** determined by ¹H NMR analysis of crude material. ^bCombined yield of diastereomeric products **18** isolated by chromatography.

performed on an analogous but simpler fused seven-membered cyclic ether that lacked the methyl substituent on the enone.¹¹

Now that the degree of substrate control had been established by use of an achiral catalyst to promote allylation, Tsuji–Trost reactions were performed with palladium catalysts prepared from the enantiomerically pure chiral PHOX ligands **17a** and **b** in order to discover whether it is possible to bias the reaction in favor of the required diastereomer **18a**. The relative configuration of the stereogenic centers in the chiral tricyclic substrate **16** meant that in each case the catalyst and substrate chirality were matched at one site of allylation and mismatched at the other. However, at the outset it was not clear if the stereochemical outcome of the allylation reaction at one site would influence the level of stereocontrol at the other site. In the case of the reaction mediated by the complex of (*S*)-ligand **17a**, an excellent level of diastereocontrol (89:11; {**18a** + **18b**}:**18c**) was obtained for allylation of the eight-membered cyclic ether as a consequence of the matching of the catalyst and substrate (entry 2, Table 1). In the case of the seven-membered ring, a 51:49 ratio of isomers was obtained favoring the required *R* configuration at the newly formed stereogenic center. Thus, the mismatch between the catalyst and substrate had completely eroded substrate control (originally 90:10 in favor of the *R* configuration) in the seven-membered ring. The situation was reversed when the reaction was performed with the palladium complex of the (*R*)-ligand **17b** (entry 3, Table 1). Complete control of the configuration of the stereogenic center on the seven-membered ring was achieved, and the diastereomers **18a** and **18c** (37:63 ratio) were produced, which differed in their configuration at the stereogenic center in the eight-membered ring. In this case, the level of intrinsic diastereocontrol in the eight-membered ring was lower and so the catalyst was able to over-ride this weak substrate bias to a significant extent.

To complete catalyst screening, we also performed an allylation reaction mediated by the palladium complex generated from a racemic mixture of ligands **17a/b** (entry 4, Table 1). The tricyclic substrate **16** is chiral, and it is conceivable that the stereochemical outcome of the reaction might be different when a racemic catalyst is used instead of an achiral catalyst, particularly if the carbonate groups in the chiral substrate **16** react with the enantiomers of the racemic catalyst at different rates. The product distribution obtained from the reaction mediated by the racemic catalyst was similar but not identical to that produced when the reaction was performed using the achiral catalyst (entry 1, Table 1). However, differences in the product distribution obtained from the two reactions (entries 1 and 4, Table 1) are relatively small and could arise either from structural differences between the

achiral and racemic catalysts or measuring errors when determining the ratios of products by ¹H NMR analysis, so it is unclear whether the differences are significant or not.

In summary, we have shown that the IJK fragment **18a** of the polyether natural product CTX3C can be prepared from a simple monocyclic precursor **12** in a concise and efficient manner by use of a four-step bidirectional sequence that involves RCM, alcohol oxidation, enol carbonate formation, and palladium-mediated Tsuji–Trost allylation. The double allylation reaction can be directed to give either **18a** and **18b** or **18a** and **18c**, by selection of the appropriate PHOX ligand (**17a** or **17b**), but it is not possible to obtain the diastereomer **18a** with high selectivity. This finding suggests that in order to obtain the required diastereomer **18a** selectively, it will be necessary to conduct the Tsuji–Trost allylation reactions sequentially instead of simultaneously, or perform epimerization of the mixture of diastereomers produced by the double allylation reaction.²⁶

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c01238>.

Full experimental details for the preparation of all new compounds and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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(19) The propyl substituents in **11b** were selected because reaction of the *bis*-ylide **10** with a relatively nonvolatile simple aldehyde (butanal) delivered the highest yields of **11**.

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(21) A complex mixture of unidentifiable products was obtained from the RCM reaction.

(22) The diol **12** was obtained as a mixture of the four possible diastereomers in approximately equivalent amounts. The good yield obtained for the RCM and oxidation sequence suggests that all four diastereomers underwent RCM, but the precise ratio of isomers was not determined prior to the oxidation reaction.

(23) RCM reactions of the diol **12** were performed in toluene at a concentration of 1 mM.

(24) Formation of the *O*-acylation product arising from competitive γ -deprotonation of the methyl substituent was not observed.

(25) The diastereomer **18d**, which is expected to be the least kinetically accessible and the least thermodynamically stable of the four possible diastereomers of **18**, was not isolated from any of the allylation reactions.

(26) Treatment of the close analogue of diketone **18** that lacks the K-ring methyl substituent with DBU in toluene produced a mixture of two diastereomers (6:1 ratio) favoring the isomer with the required configuration.