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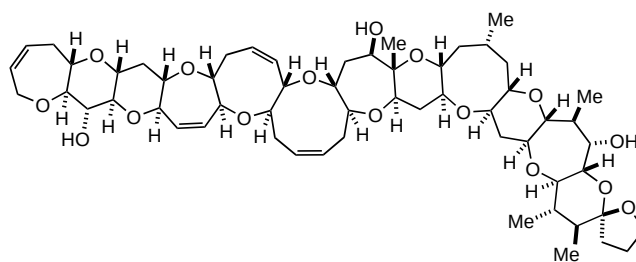
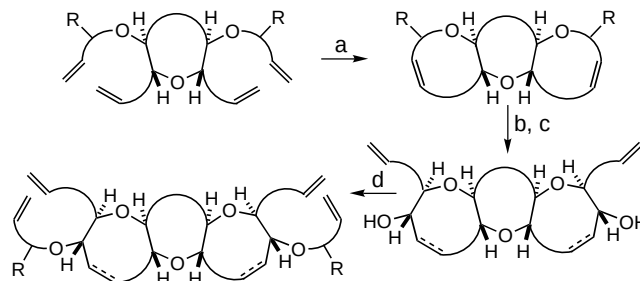


Figure 1. The structure of CTX-3C.

targets, providing a stimulus for the development of many new reactions and strategies for the construction of polycyclic systems.^[3] This work has culminated in the recent total syntheses of brevetoxins A and B, completed by Nicolaou and co-workers,^[4] as well as several syntheses of the smaller congener hemibrevetoxin B.^[5]

We recently presented a powerful strategy for the construction of subunits found in the brevetoxins and ciguatoxins. Catalytic ring-closing metathesis (RCM)^[6] reactions of enol ethers,^[7a,b] allylic ethers,^[7c,d] or alkynyl ethers^[7e] were promoted by the Schrock catalyst [2,6-*i*Pr₂C₆H₃NMo{OC(CF₃)₂-Me}₂CHCMe₂Ph] (**1**)^[8] or the Grubbs catalyst [Cl₂{(C-C₆H₁₁)₃P}₂-RuCHPh] (**2**)^[9] leading to the formation of cyclic ethers.^[10] Stereoselective elaboration of the RCM products then gave fully functionalized, saturated or unsaturated, cyclic ethers suitable for conversion into polyoxacyclic units of the type found in the natural products.^[7d]

We now report a new strategy for polycyclic ether assembly, the essence of which is illustrated in Scheme 1.^[11] We envisaged the construction of rings in a two-directional



Scheme 1. Strategy for the synthesis of polycyclic ethers using two-directional RCM reactions. a) Ring-closing metathesis; b) ring functionalization; c) side-chain functionalization; d) side-chain introduction.

manner by performing double RCM reactions of allylic ethers, enol ethers, or alkynyl ethers, or any combination thereof.^[12] We expected that the reaction would be of general applicability, permitting the preparation of tricyclic ethers with any permutation of ring sizes. Elaboration of the tricyclic products, using our recently described methods,^[7b] followed by side-chain functionalization would then provide appropriately functionalized systems for iteration of the two-directional ring-closure sequence.

The precursors were prepared as shown in Scheme 2. Treatment of commercially available tri-*O*-acetyl-D-glucal (**3**) with sodium methoxide afforded D-glucal, which was converted into 4,6-*O*-di-(*tert*-butyl)silanediy-D-glucal accord-

Synthesis of Polycyclic Ethers by Two-Directional Double Ring-Closing Metathesis**

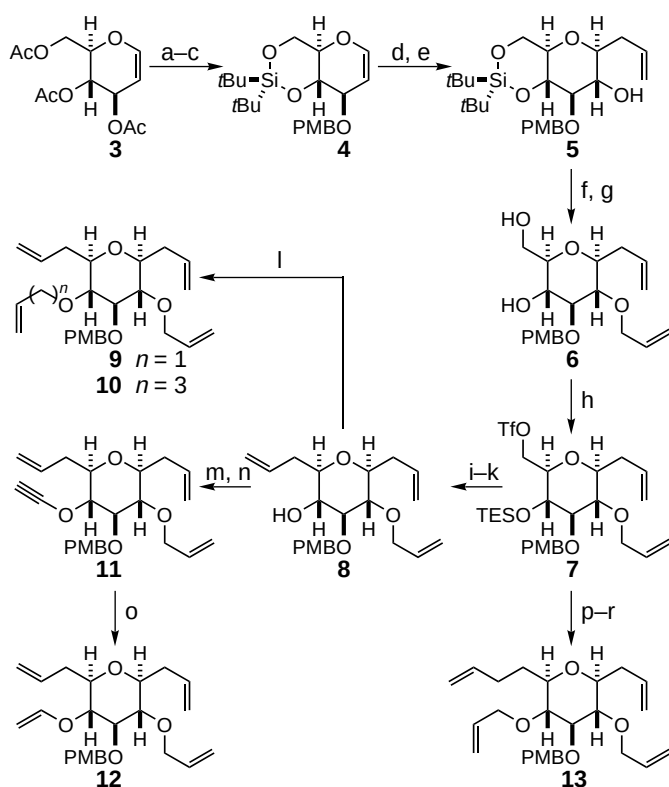
J. Stephen Clark* and Olivier Hamelin

Neurotoxic marine polycyclic ethers of the brevetoxin and ciguatoxin family continue to be interesting synthetic targets as a consequence of their architectural complexity and potent biological activity.^[1] They constitute a major challenge in terms of medium-size ring construction as illustrated by CTX-3C (Figure 1).^[2] This ciguatoxin contains a total of 13 rings and possesses a daunting combination of saturated and unsaturated medium-sized rings. The size of the brevetoxins and ciguatoxins, coupled with their structural and stereochemical complexity, has made them irresistible synthetic

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Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



Scheme 2. Preparation of cyclization precursors for two-directional RCM reactions. a) NaOMe, MeOH, RT, 92–100%; b) $t\text{Bu}_2\text{Si}(\text{OTf})_2$ (1.05 equiv), DMF, pyridine -40°C , 92%; c) PMBOC(NH) CCl_3 (2.5 equiv), PPTS, CH_2Cl_2 , reflux, 94%; d) Me_2CO_2 , Me_2CO , CH_2Cl_2 , 0°C ; e) $\text{CH}_2\text{CHCH}_2\text{MgBr}$ (3 equiv), ZnCl_2 (3 equiv), THF/ Et_2O (2/1), $-78 \rightarrow 5^\circ\text{C}$, 73% over 2 steps ($>20:1$); f) NaH (1.6 equiv), $\text{CH}_2\text{CHCH}_2\text{Br}$ (1.15 equiv), $n\text{Bu}_4\text{NI}$, [18]crown-6, THF, RT; g) TBAF (5 equiv), THF, RT, 81% over 2 steps; h) TiF_4 (1.15 equiv), TESOTf (1.5 equiv), 2,6-lutidine (5 equiv), CH_2Cl_2 , -78°C ; i) $\text{Me}_3\text{SiCCl}_2$ (6 equiv), THF/HPMA (6/1), $-78^\circ\text{C} \rightarrow \text{RT}$; j) TBAF (3 equiv), THF, RT, 82% over 3 steps; k) H_2 , Lindlar catalyst, EtOAc, RT, 83%; l) NaH, $\text{CH}_2\text{CH}(\text{CH}_2)_n\text{Br}$ ($n=1, 3$), $n\text{Bu}_4\text{NI}$, [18]crown-6, THF, RT, 90% **9**, 81% **10**; m) KH (5 equiv), Cl_2CCHCl (1.3 equiv), THF, $-78^\circ\text{C} \rightarrow \text{RT}$; n) $n\text{BuLi}$ (5 equiv), Et_2O , $-78 \rightarrow -20^\circ\text{C}$, 82% over 2 steps; o) H_2 , 5% Pd/BaSO₄, pyridine, RT, 70%; p) $\text{CH}_2\text{CHCH}_2\text{MgBr}$ (5 equiv), CuBr (0.78 equiv), Et_2O , 0°C , 91% over 2 steps; q) TBAF (1.2 equiv), THF, RT, 90%; r) NaH (2 equiv), $\text{CH}_2\text{CHCH}_2\text{Br}$ (1.5 equiv), $n\text{Bu}_4\text{NI}$, THF, RT, 85%. RT=room temperature, PMB=*p*-methoxybenzyl, PPTS=pyridinium *p*-toluenesulfonate, TBAF=tetrabutylammonium fluoride, TiF_4 =trifluoromethanesulfonic anhydride, TESOTf =triethylsilyl trifluoromethanesulfonate, HMPA=hexamethyl phosphoramide.

ing to the procedure of Hoberg.^[13] The free secondary hydroxyl group was then protected as the *p*-methoxybenzyl (PMB) ether to afford the dihydropyran **4**.^[14] Epoxidation of the enol ether using dimethyldioxirane gave an unstable glacial epoxide.^[15] Immediate treatment of the epoxide with allylmagnesium bromide in the presence of zinc chloride provided the alcohol **5** in a highly diastereoselective manner ($>20:1$ as indicated by NMR analysis).^[16] Allylation of the free hydroxyl group and subsequent removal of the silicon protecting group delivered the diol **6** in good yield. One-pot triflate formation at the primary hydroxyl site and protection of the secondary hydroxyl group as the triethylsilyl (TES) ether afforded the triflate **7**.^[5d] Introduction of the side chain was accomplished by treatment of triflate **7** with lithium

trimethylsilylacetylide.^[10f] Removal of the silicon protecting groups and subsequent Lindlar hydrogenation delivered the alcohol **8**.

The RCM precursors selected for study were prepared from the triflate **7** and the alcohol **8**. The bis-allyl ether **9** and the precursor **10** were obtained by deprotonation of the alcohol **8** and treatment of the resulting sodium alkoxide with allyl bromide and 5-bromopent-1-ene, respectively. The alkynyl ether **11** was prepared from **8** using the procedure of Greene and co-workers,^[17] which we recently employed in the preparation of related compounds.^[7e] Hydrogenation of the alkynyl ether **11** then afforded the enol ether **12** in good yield.^[18] The final precursor required for our study, the bis-allyl ether **13**, was prepared in a direct and efficient manner by copper-catalyzed addition of allylmagnesium bromide to the triflate **7**,^[19] removal of the TES protecting group, and conversion of the free hydroxyl group into the allyl ether.

The two-directional double RCM reactions of the precursors **9**–**13** were investigated and the relative efficacy of the molybdenum catalyst **1** and the ruthenium catalyst **2** was compared in each case (Table 1). The double allylic ether RCM reaction of the *meso* substrate **9**, when performed with either of the catalysts, led to the efficient formation of two seven-membered rings. The resulting crystalline tricyclic ether

Table 1. Double RCM reactions of substrates **9**–**13** mediated by complexes **1** and **2**.

Substrate	Catalyst ^[a]	Yield [%] ^[b]	Product
9	1 (35 mol %)	85	
9	2 (25 mol %)	88	
10	1 (50 mol %)	21	
10	2 (30 mol %)	65	
11	2 (15 mol %)	50	
12	1 (20 mol %)	63	
12	2 (30 mol %) ^[c]	71	
13	1	— ^[d]	
13	2 (20 mol %)	77	

[a] Reaction conditions: complex **1** in benzene at room temperature or 55°C , complex **2** in dichloromethane at room temperature or reflux. [b] Yield of product after chromatographic purification. [c] Reaction performed in benzene at reflux. [d] A complex mixture of products was isolated.

14 was obtained in good yield, and its structure was confirmed by X-ray analysis. Treatment of the homologous compound **10** with the catalyst **2** resulted in formation of a seven-membered and a nine-membered ring by allylic ether and alkene RCM, yielding tricyclic ether **15** in good yield. Treatment of the same substrate with the molybdenum catalyst **1** provided the product in inferior yield. Simultaneous allylic ether and enyne RCM reactions were accomplished upon treatment of the substrate **11** with catalyst **2**, and the diene **16**, which corresponds to the ABC ring system found in CTX-3C (Figure 1), was produced in reasonable yield. Treatment of the substrate **12** with either catalyst **1** or **2** led to simultaneous RCM of an allylic ether and an enol ether, and afforded the product **17** in good yield. The success of the ruthenium-catalyzed reaction is particularly noteworthy because enol ethers are not usually good substrates for the catalyst **2**.^[20] Finally, formation of a seven- and an eight-membered ring by double RCM was accomplished by treatment of the substrate **13** with the catalyst **2** to yield product **18**.

Our results demonstrate that it is possible to build outwards from a single ring in a two-directional manner by performing double RCM reactions. In all cases the yields of the *trans*-fused tricyclic ethers ranged from good to excellent, and no bridged cyclic ethers, arising from the other possible intramolecular double RCM manifold, were isolated.^[12d] It is remarkable that higher yields were obtained when the ruthenium catalyst **2** was used instead of the generally more reactive molybdenum catalyst **1**.

This efficient and flexible two-directional strategy for the construction of *trans*-fused polyoxacyclic frameworks is currently being utilized to construct subunits of the brevetoxins and ciguatoxins.

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