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Synthesis of Brevetoxin Sub-units by Sequential Ring-closing Metathesis and Hydroboration

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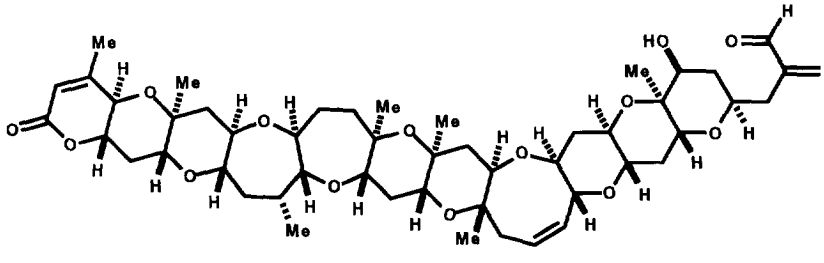
Abstract: A new strategy for the construction of polycyclic ethers by sequential ring-closing metathesis and stereoselective hydroboration has been explored. This sequence of reactions has been used to prepare bicyclic ethers corresponding to sub-units of brevetoxin B.

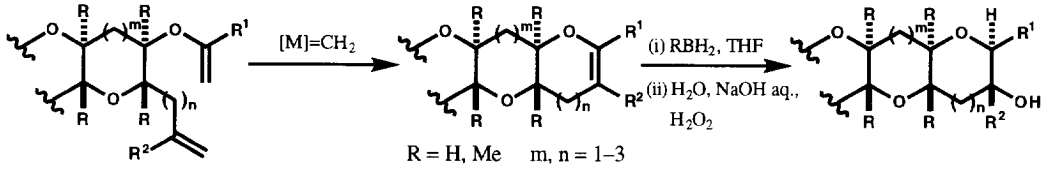
The marine neurotoxin brevetoxin B, was isolated from the dinoflagellate *Gymnodinium breve* Davis and characterised by Nakanishi and co-workers in 1981.[1] This compound was just the first of a large group of structurally related marine natural products to be identified.[2] As a consequence of the elegant structural features and the synthetic challenges presented by the brevetoxins and related marine toxins such as the ciguatoxins,[3] gambierol,[4] the gambieric acids,[5] yessotoxin,[6] and maitotoxin,[7] these compounds have attracted considerable attention, and have provided the impetus for the development of a range of powerful synthetic methods for the construction of cyclic ethers.[8] This work has culminated in the recent impressive total synthesis of brevetoxin B completed by Nicolaou and co-workers,[9] and two syntheses of the smaller congener hemibrevetoxin B, accomplished by Nicolaou and Yamamoto.[10]



Brevetoxin B

Figure 1

In spite of recent advances in the synthesis of cyclic ethers, there is still no general and convergent strategy for the assembly of large fused polycyclic ether arrays. In order to address this problem, we sought to develop an efficient general approach to the synthesis of polyoxacycles in which catalytic ring-closing metathesis and subsequent stereoselective hydroboration would be used to construct *trans*-fused cyclic ethers (**Scheme 1**).[11,12] We were attracted by this approach because, in principle, it could be used in an iterative sense, permitting sequential ring construction to be accomplished at the rate of four or five steps per ring. In the following pages, we report our progress towards this objective.



Scheme 1

Prior to our work in this area, Grubbs had shown that it was possible to prepare five- and six-membered ethers by intramolecular metathesis of alkenes with enol ethers using the molybdenum catalyst **1** (**Figure 2**).[13] The aim of the preliminary studies described herein, was to demonstrate that this reaction could be used to prepare fused bicyclic enol ethers possessing six-membered or larger rings, and that subsequent stereoselective hydroboration of these compounds would provide *trans*-fused bicyclic ether units of the type found in the brevetoxins. While our studies were in progress Nicolaou reported that olefinic esters could be converted directly to six- and seven-membered enol ethers by tandem methylenation and metathesis using excess Tebbe reagent,[14] and it is this report which has prompted us to disclose our preliminary results at this time.

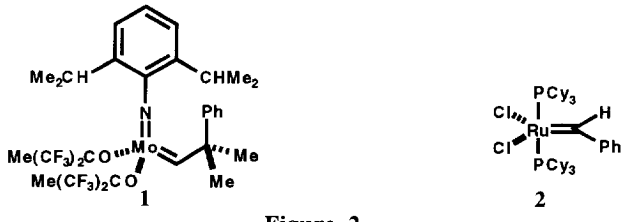
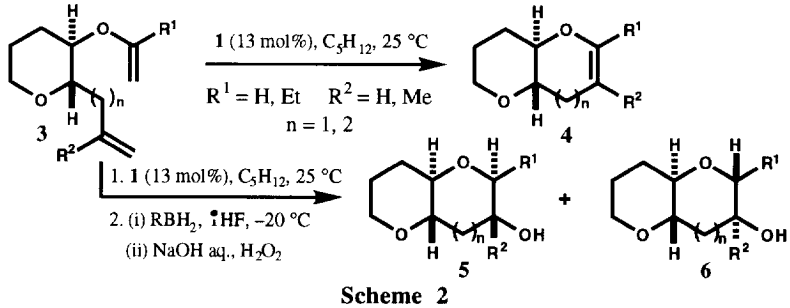


Figure 2

Initial synthetic studies were directed towards the construction of 6,6- and 6,7-bicyclic ethers shown in **Scheme 2**. The enol ethers **3** were prepared in good yield from the corresponding esters using Takai's method.[15] Treatment of the cyclisation precursors **3a-f** with a catalytic amount (13 mol%) of the complex **1**,[16] afforded the cyclic enol ethers **4a-f** in good yield, even though these compounds were volatile and tended to undergo partial hydrolysis upon purification by chromatography (**Table**). Disubstituted and trisubstituted enol ethers were prepared by ring-closing metathesis, the highest yields (>90%) being obtained upon cyclisation of the substrates **3c** and **3f** (**Table**). Efficient conversion of the enol ethers **4a-f** to the required alcohols **5a-f** was accomplished by hydroboration (**Table**).[12] High levels of diastereocontrol were achieved when thexyl borane was used as the hydroborating agent at low temperature (–20 °C), but reagent stoichiometry had a profound effect on reaction yields.[17] It was possible to hydroborate the cyclic enol ethers **4** directly after the ring-closing metathesis reaction, in order to avoid the purification and prolonged handling of these acid-sensitive intermediates. The yields of the bicyclic ethers prepared in this way were generally high, and those obtained for the alcohols **5b** and **5e** were particularly significant (**Table**). In general, the yields of the alcohols **5a** and **5d**, produced by hydroboration of the disubstituted enol ethers **4a** and **4d**, were rather modest, and substantial amounts of ring-opened products were obtained from these reactions (**Table**).[17]



Scheme 2

Substrate	n	R^1	R^2	%4[a]	RBH_2	%(5+6)[a]	5:6[c]
3a	1	H	H	63	$ThxBH_2$	52	—[d]
3b	1	Et	H	72	$ThxBH_2$	61[b]	—[d]
3c	1	H	Me	93	BH_3.THF	67[b]	62:38
3d	2	H	H	64	$ThxBH_2$	43[b]	90:10
3e	2	Et	H	42	$ThxBH_2$	41[b]	—[d]
3f	2	H	Me	94	BH_3.THF	0	—

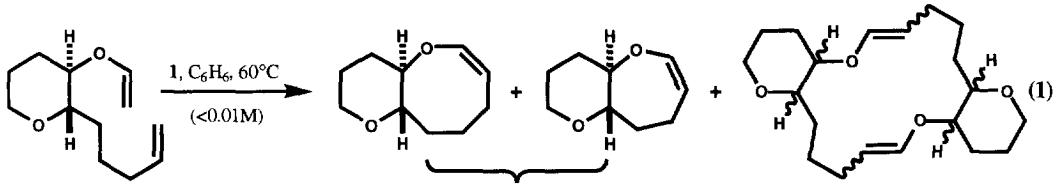
a Yield of isolated material after purification by chromatography. *b* Combined yield of products (**5**+**6**) obtained without purification of the intermediate enol ether **4**. *c* The ratio of products (**5**:**6**) was determined by analysis of the nmr spectra of the crude reaction material. *d* The diastereomer **5** was isolated exclusively.

Table

The ruthenium complex **2** (**Figure 2**) was also explored as a catalyst for the ring-closing metathesis of the substrates **3a-f.** This complex is much easier to prepare and handle than the molybdenum complex **1**,[18] and Grubbs has demonstrated the synthetic utility of this and related ruthenium complexes as catalysts for the preparation of heterocycles and carbocycles by ring-closing metathesis.[19] Unfortunately, this complex proved to be completely ineffective for the cyclisation of the enol ethers **3**.[13]

The preparation of tetrasubstituted bicyclic enol ethers such as **4** (R^1 = Et, R^2 = Me, **Scheme 2**) by ring-closing metathesis was also explored. However, the precursors **3** (R^1 = Et, R^2 = Me, **Scheme 2**) failed to cyclise under the reaction conditions investigated. Although Grubbs has demonstrated that it is possible to prepare tetrasubstituted cycloalkenes by ring-closing metathesis,[20] the relatively low reactivity of enol ethers combined with unfavorable steric interactions associated with the formation of tetrasubstituted systems seems to preclude intramolecular cyclisation of these substrates.

It also proved possible to prepare 6,8-bicyclic systems by ring-closing metathesis of enol ethers (**eq. 1**), although the yields were lower than those of the 6,6- and 6,7-bicyclic enol ethers. Treatment of the vinyl ether **7** with the molybdenum complex **1** (15 mol%) under high dilution conditions afforded an inseparable mixture of the required cyclic ether **8** and the 6,7-bicyclic system **4d** in a combined yield of 40% (~2:1 ratio), along with an equivalent amount of the cyclo-dimer **9**. The isolation of the 6,7-bicycle **4d** from this reaction was somewhat surprising, and it is likely that this compound is formed by isomerisation of the vinyl ether **7** prior to metathesis.[21]



7 **8** 40% (~2:1) **4d** **9**

Our results demonstrate that ring-closing metathesis of enol ethers with alkenes and subsequent stereoselective hydroboration can be used to prepare 6,6- and 6,7-bicyclic ethers, but that the reaction is of limited use for the construction of 6,8-bicyclic ethers or tetrasubstituted enol ethers. In the following paper we describe a successful alternative approach to the preparation of medium-ring ethers using catalytic ring-closing metathesis to effect ring construction.

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