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Enantioselective Synthesis of Medium-ring Sub-units of Brevetoxin A by Ring-closing Metathesis

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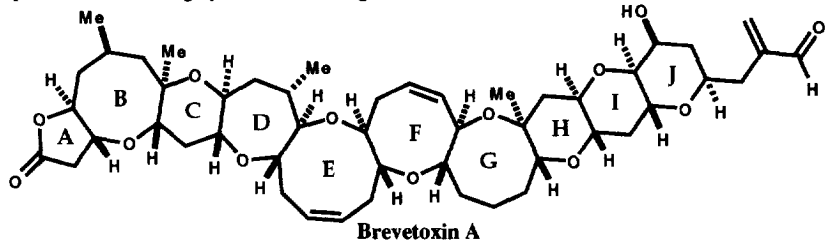
Abstract: A new strategy for the enantioselective synthesis of eight- and nine-membered cyclic ethers corresponding to sub-units of brevetoxin A has been developed. The strategy involves the use of ring-closing metathesis reactions of allylic ethers to effect ring construction.

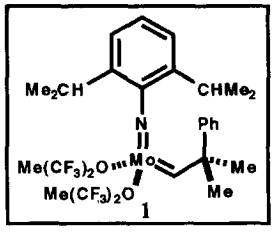
Brevetoxin A is the most potent of the ichthyotoxins that have been isolated from the dinoflagellate *Gymnodinium breve*.[1,2] Although brevetoxin A possesses a laddered ether array similar to that found in brevetoxin B, it is a far more formidable target as a consequence of the number of medium-sized cyclic ethers embedded in its structure. Brevetoxin A possesses a total of three eight-membered rings and one nine-membered ring, and rings of these sizes are notoriously difficult to construct.[3] The central DEFG system, in particular, represents a daunting synthetic challenge.



Brevetoxin A

Figure 1

In the preceding paper we disclosed a new strategy for the preparation of *trans*-fused bicyclic ethers possessing six- and seven-membered rings in which ring-closing metathesis was employed in conjunction with stereoselective hydroboration. In order to synthesise brevetoxin A, a general method for the construction of eight- and nine-membered cyclic ethers was also required. Although a simple fused eight-membered cyclic enol ether was prepared in moderate yield by direct cyclisation using the previously developed method,[4] ring-closing metathesis of the functionalised substrate **2**, promoted by the catalyst **1**,[5] failed to provide the required enol ether **3** (**eq. 1**).



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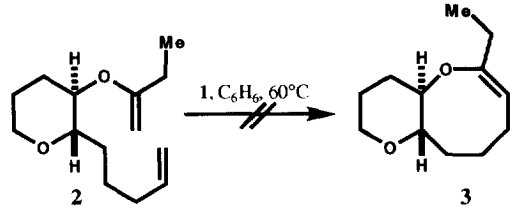
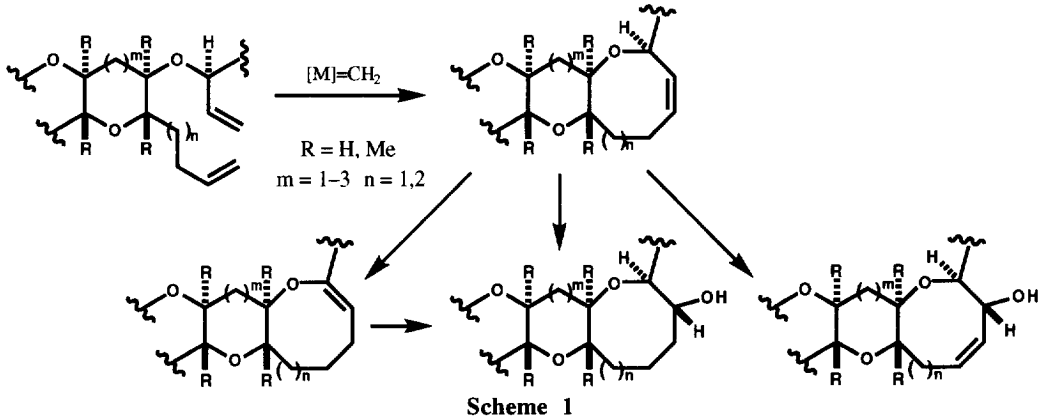


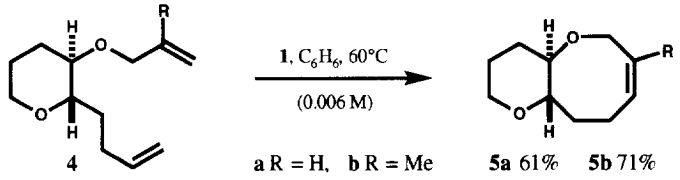
2 **3** **(1)**

In order to address the issue of medium-ring construction, an alternative route was explored, in which ring construction would be accomplished by ring-closing metathesis of allyl ethers, rather than enol ethers (**Scheme 1**).[6] The inherent advantages of this approach would be the much greater reactivity of allyl ethers in comparison to enol ethers,[7] and the greater stability of the resulting cyclic allyl ethers compared to medium-ring enol ethers. In addition, the route would be more flexible as a consequence of the greater number of options available for subsequent elaboration of the products to give sub-units of brevetoxin A (**Scheme 1**). For example, the cyclic allyl ethers could be functionalised by allylic oxidation with transposition to afford unsaturated cyclic ethers corresponding to rings E and F of brevetoxin A. Alternatively, direct hydroboration of the metathesis product or isomerisation to the enol ether and subsequent hydroboration, would provide medium-ring ethers correlating to rings B and G.



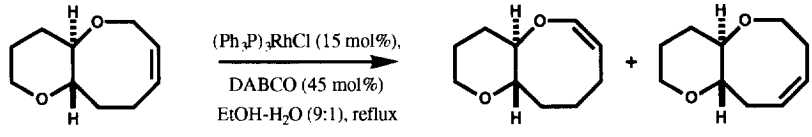
Scheme 1

The feasibility of this approach was first established by investigation of the ring-closing metathesis reactions of two model allyl ethers (**eq. 2**). Cyclisation of the allyl ethers **4a** (R = H) and **4b** (R = Me), catalysed by the complex **1**, afforded the cyclic allyl ethers **5a** and **5b** in good yield, with no evidence of competing intermolecular reactions of the type found when attempting to prepare medium-ring ethers by metathesis of enol ethers.



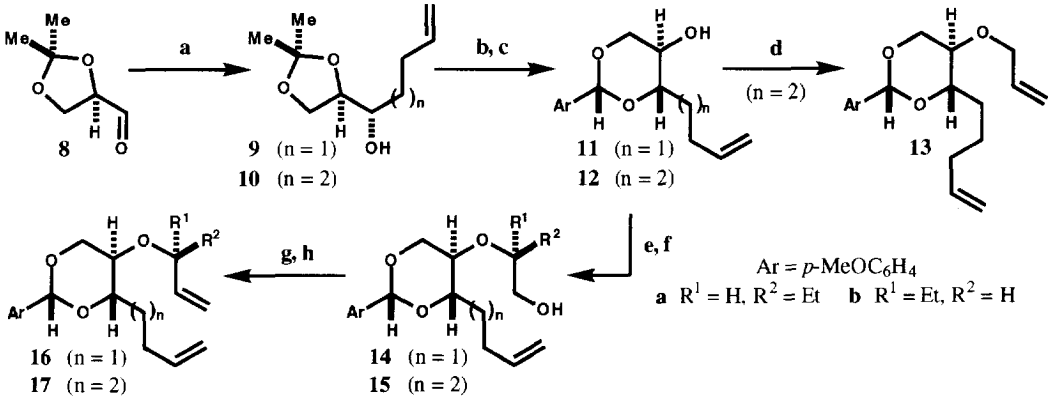
4 a R = H, b R = Me **5a** 61% **5b** 71% (2)

To demonstrate that it was possible to convert medium-ring allyl ethers to the corresponding enol ethers, isomerisation of the allyl ether **5a** into the cyclic enol **6** was explored (**eq. 3**). A variety of transition metal complexes were investigated as possible catalysts for this transformation.[8] However, the most satisfactory result was obtained using Wilkinson's catalyst under conditions originally described by Corey.[9] In this case, the required enol ether **6** was isolated in reasonable yield along with a significant amount of the regioisomeric alkene **7**. Attempted isomerisation of the allyl ether **5a** with other catalyst systems led to incomplete conversion, or afforded inferior yields and product ratios.



5a **6** 61% + **7** 20% (3)

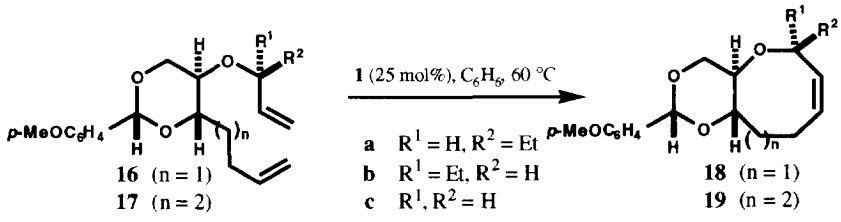
Following the successful preparation of enol ether **6** by sequential ring-closing metathesis and isomerisation, the enantioselective synthesis of eight- and nine-membered cyclic ethers was explored. Preparation of the required cyclisation precursors commenced from the readily available 'chiral pool' material (*R*)-2,3-*O*-isopropylidene glyceraldehyde (**8**) (**Scheme 2**).[10] Chelation-controlled addition of the Grignard reagent prepared from either 4-bromo-1-butene or 5-bromo-1-pentene, in the presence of zinc(II) chloride afforded the alcohols **9** and **10**, respectively,[11] as mixtures of diastereomers with the indicated isomer predominating. The acetonides **9** and **10** were converted to the acetals **11** and **12** by deprotection and subsequent acid-catalysed reprotection using *p*-methoxybenzaldehyde dimethyl acetal.[12] The alcohols **11** and **12** were then alkylated in good yield using racemic methyl 2-bromobutyrate to afford inseparable mixtures of diastereomers, and the alcohol **12** was also alkylated with allyl bromide to afford the allyl ether **13**. Reduction of the diastereomeric mixtures with lithium aluminium hydride afforded the primary alcohols (**14a/b** and **15a/b**). The diastereomeric pairs of alcohols were separable by chromatography, and were independently converted to the allyl ethers (**16a**, **16b**, **17a**, and **17b**) required for ring-closing metathesis.



Reagents: **a** $CH_2CHCH_2(CH_2)_nMgBr$, $ZnCl_2$, -90 °C, Et_2O (**9a** 76%, ~10:1, **9b** 72%, ~5:1); **b** PPTS, MeOH, reflux (**9**), or CF_3CO_2H, THF-H_2O, reflux (**10**); **c** *p*-$MeOC_6H_4CH(OMe)_2$, CSA, DMF, 80 °C (**11** 59%, **12** 60%, 2 steps); **d** NaH, CH_2CHCH_2Br, DMF rt (85 %); **e** NaH, (±)-$EtCH(Br)CO_2Me$, DMF, rt (n = 1 93%, n = 2 83%); **f** $LiAlH_4$, Et_2O, reflux (**14a+b** 86%, **15a+b** 84%); **g** SO_3.pyr, Et_3N, DMSO-CH_2Cl_2, rt; **h** $Ph_3P^+MeBr^-$, *n*-BuLi, THF, rt (**16a** 60%, **16b** 76%, **17a** 35%, **17b** 55%, 2 steps).

Scheme 2

The ring-closing metathesis reaction of each of the allyl ethers (**16a**, **16b**, **17a**, **17b** and **13**), mediated by the molybdenum catalyst **1** (**eq. 1**), was then investigated (**eq. 4**). Three of the substrates examined underwent ring closure in excellent yield under moderately high dilution conditions (**Table**). However, the ring-closing metathesis reaction of the precursor **17b** afforded the cyclic ether **19b** in very low yield, in marked contrast to the result obtained with the diastereomeric precursor **17a**. The differing behaviour of substrates **17a** and **17b** was unexpected, and may due to unfavourable interactions between the ethyl substituent and transannular groups in the transition state for cyclisation of the allyl ether **17b**.[13]



(4)

substrate	n	R^1	R^2	conc.	product	% yield[a]
16a	1	H	Et	0.008 M	**18a**	97
16b	1	Et	H	0.008 M	**18b**	86
17a	2	H	Et	0.003 M	**19a**	86
17b	2	Et	H	0.003 M	**19b**	14 (17)[b]
17c (13)	2	H	H	0.003 M	**19c**	58

a Isolated yield of product after purification by column chromatography. *b* Yield of product based on recovered substrate.

Table

The results of the ring-closing metathesis reactions demonstrate that a general enantioselective route to medium-ring ethers of the type found in brevetoxin A is possible using this approach. We are currently investigating the further elaboration of the cyclic allyl ethers such as **18a** and **19a**, and the results of these studies will be reported in due course.

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