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Synthesis of alkenyl-substituted cyclic enol ethers by catalytic ring-closing metathesis of alkynyl ethers

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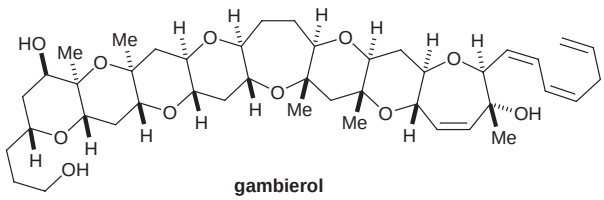
Ring-closing enyne metathesis can be used to prepare alkenyl-substituted six- and seven-membered cyclic enol ethers in moderate to good yield.

Over the past two decades, fused polycyclic ether natural products, such as the brevetoxins and the ciguatoxins,[1] have attracted considerable attention because of their fascinating structures and potent biological activities.[2] Many of the natural products of this type possess arrays of *trans*-fused six- and seven-membered cyclic ethers, as exemplified by gambierol.[3]



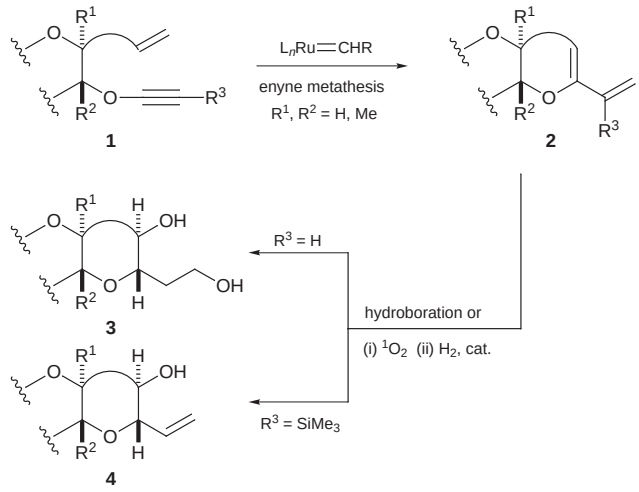
gambierol

Recently, we[4] and others[5] have found that ring-closing metathesis reactions offer a powerful and general approach to the synthesis of cyclic ether sub-units found in the brevetoxins and ciguatoxins. We have demonstrated that the sequence of ring-closing metathesis[6] and hydroboration can be used to prepare six- and seven-membered cyclic ethers[4a] and that ring-closing metathesis of allylic ethers[4b] can be used to prepare eight- and nine-membered cyclic ethers in excellent yield.

In connection with our continuing studies directed towards the synthesis of the brevetoxins and the ciguatoxins, we became interested in exploiting ring-closing enyne metathesis reactions to complement the enol ether and allylic ether ring-closing metathesis reactions that we have already developed.[4] Our interest in the use of ring-closing enyne metathesis reactions was stimulated by recent promising reports from the groups of Murai,[7] Mori,[8] and Barrett and Gibson[9] who have described the preparation of carbocycles and nitrogen heterocycles using ruthenium-catalysed enyne metathesis reactions.

The general strategy for the preparation of sub-units of the brevetoxins and ciguatoxins using a ring-closing enyne metathesis reaction is shown in Scheme 1. We envisaged subjecting a suitably functionalised alkynyl ether **1** to a ruthenium-catalysed ring-closing metathesis reaction to obtain the alkenyl-substituted enol ether **2**. Elaboration of this product (R^3 = H) by hydroboration or by reaction with $^1O_2$ and hydrogenation of the resulting cyclic peroxide,[10] would provide the diol **3**. Application of the same reactions to the vinylsilane-substituted cyclic enol ether **2** (R^3 = SiR_3) would afford the vinyl-substituted cyclic ether **4** by Peterson elimination of the resulting β-hydroxy silane.[11] The pendant vinyl group of this compound would then provide scope for construction of an additional cyclic ether by a subsequent ring-closing metathesis reaction.

We wanted to ascertain whether alkynyl ethers would undergo reaction with the Grubbs catalyst, $Cl_2Ru(PCy_3)_2$-CHPh,[12] in contrast to enol ethers, which were unreactive to this catalyst or the metal alkylidenes generated from it. We also wanted to determine whether terminal alkynyl ethers would



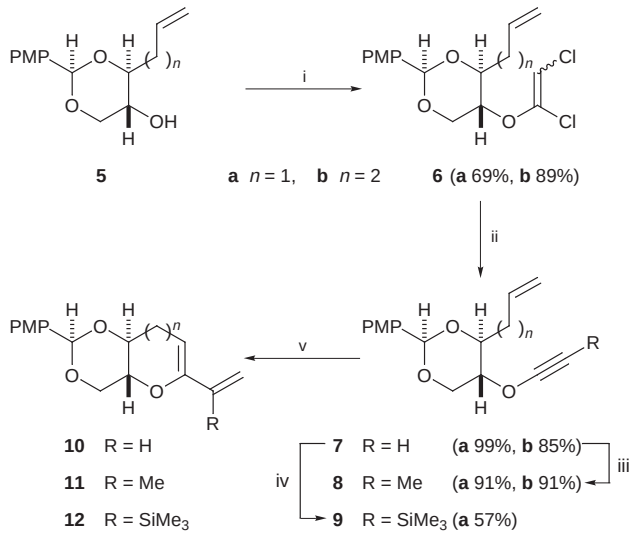
Scheme 1

undergo efficient ring-closing metathesis because there was evidence to suggest that terminal alkynes are not generally good substrates for this reaction.[8,9]

The alkynyl ethers required for our study were prepared from the alcohols **5a** and **5b**, which are readily available from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (Scheme 2).[4b,13] The cyclisation substrates **7a** and **7b** were prepared by an adaptation of Greene's method for the synthesis of alkynyl ethers.[14] This method involves deprotonation of an alcohol with KH and reaction of the resulting alkoxide with Cl_2C=CHCl to give a mixture of dichloro enol ethers that are then converted to the required alkynyl ether by treatment with *n*-butyllithium.[14] Greene has demonstrated that this sequence of reactions can be performed in a one-pot fashion without isolation and purification of the intermediate dichloro enol ethers, and that it can be used to convert hindered secondary alcohols into alkynyl ethers.

Initially, we used Greene's one-pot procedure to convert the alcohols **5a** and **5b** to the required alkynyl ethers **7a** and **7b**. However, only modest yields of the products were obtained, so we opted to isolate the dichloro enol ethers produced upon reaction of Cl_2C=CH_2 with the sodium alkoxides generated from the alcohols **5a** and **5b**. Enol ether formation proceeded in reasonable yield and the products **6a** and **6b** were isolated as stable crystalline solids. Treatment of these dichloro enol ethers with *n*-butyllithium provided the alkynyl ethers **7a** and **7b** in very high yield. The yields over two steps, including isolation of the intermediate dichloro enol ethers, were only marginally lower those obtained by Greene when he used his one-pot procedure for the preparation of related systems.[14]

Having prepared the ethers **7a** and **7b**, we then obtained the other substrates of interest by alkylation of these terminal alkynes. Thus, the substrates **8a** and **8b** were prepared by deprotonation of the alkynyl ethers **7a** and **7b** followed treatment with methyl iodide, and the silyl-substituted alkynyl



Scheme 2 *Reagents and conditions*: i, NaH, THF, rt, then $CHClCCl_2$ (3 equiv.), −50 °C→rt; ii, *n*-BuLi, Et_2O, −78 °C→rt; iii, *n*-BuLi, DMPU, −78 °C, Et_2O, then MeI, −10 °C→rt; iv, *n*-BuLi, Me_3SiCl, Et_2O, −78 °C→rt; v, $Cl_2Ru(PCy_3)_2CHPh$ (10 mol%), CH_2CH_2 (10 min), CH_2Cl_2, rt or reflux, 4 h or 14 h.

ether **9a** was prepared by deprotonation of the alkyne **7a** and reaction of the resulting anion with trimethylsilyl chloride.

The ring-closing metathesis reactions of the alkynyl ethers **7**–**9** were explored (Scheme 2). Treatment of each substrate with the Grubbs catalyst, $Cl_2Ru(PCy_3)_2CHPh$,[12] in CH_2Cl_2 at reflux led to successful ring-closing metathesis and afforded the alkenyl-substituted cyclic enol ethers **10**–**12** (Table 1).† The highest yields for the ring-closing enyne metathesis reaction were obtained upon cyclisation of the alkynyl ethers **7a** and **8a** to give the six-membered cyclic enol ethers **10a** and **11a**. Interestingly, the terminal alkynyl ether **7a** underwent efficient cyclisation, although a higher yield was obtained upon reaction of the substrate **8a**, containing a non-terminal alkyne. The silyl-substituted alkynyl ether **9a** also underwent cyclisation, but in low yield; it is likely that the poor yield for this reaction can be attributed to the steric bulk of trimethylsilyl substituent.[8a]

The ring-closing enyne metathesis reactions to produce seven-membered cyclic enol ethers proved to be less successful than those to produce the alkenyl-substituted dihydropyrans. The reactions were slow, and prolonged reaction times were required for complete reaction. There was little difference between the yield obtained upon cyclisation of the terminal alkynyl ether **7b** to give the diene **10b** and that obtained upon cyclisation of the methyl-substituted substrate **8b** to give the diene **11b**.

In all the enyne metathesis reactions, the ruthenium catalyst was 'pre-activated' by the passage of ethene through the solution of the catalyst prior to addition of the substrate, and reactions were then performed under an atmosphere of ethene. Inferior yields were obtained upon cyclisation of the substrates **7b** and **8b** when the reactions were performed in the absence of ethene.

Table 1 Results of ring-closing enyne metathesis reactions of the alkynyl ethers **7**–**9** catalysed by $Cl_2Ru(PCy_3)_2CHPh$ (10 mol%)

Substrate	Reaction time/h	Product	Yield (%)[a]
7a	4[b]	**10a**	65
7b	14[c]	**10b**	33
8a	4[b]	**11a**	77
8b	14[c]	**11b**	27
9a	4[b]	**12a**	20

[a] Yield of isolated product after chromatography on silica gel. [b] Reaction performed in CH_2Cl_2 at reflux. [c] Reaction performed in CH_2Cl_2 at room temperature.

Our results show that ring-closing metathesis of alkynyl ethers can be used to prepare alkenyl-substituted cyclic enol ethers. Although the yields of seven-membered cyclic enol ethers were low, we have demonstrated that the reaction is a synthetically viable one for the preparation of alkenyl dihydropyrans in good yield. We have also shown that the Grubbs catalyst, $Cl_2Ru(PCy_3)_2CHPh$,[12] can be used for ring-closing enyne metathesis of alkynyl ethers, which contrasts with the lack of reactivity exhibited by this catalyst towards related enol ethers.[4a,15]

The cyclic ethers **10a** and **10b** are potentially useful enantiomerically pure chiral building-blocks for the synthesis of sub-units of the brevetoxins and ciguatoxins. The elaboration of these compounds (*e.g.* **2**→**3**) is currently under investigation, and the results of these studies will be reported in due course.

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Notes and references

† Typical procedure for the ring-closing enyne metathesis of the substrates **7**–**9**: The catalyst, $Cl_2Ru(PCy_3)_2CHPh$ (38 mg, 0.045 mmol, 10 mol%), was dissolved in dry CH_2Cl_2 (60 mL) and a stream of ethene passed through the solution for 10 min (the solution turned from purple to orange in colour). A solution of the alkyne (0.45 mmol) in dry CH_2Cl_2 (5 mL) was added by cannula to the solution of the catalyst under an atmosphere of ethene at room temperature. The flask was then washed with further CH_2Cl_2 (3 mL) and this was added to the reaction mixture. The mixture was then stirred under a static atmosphere of ethene at reflux (4 h) or room temperature (21 h). On completion of the reaction, the solvent was then removed *in vacuo* and the residual material was purified by flash column chromatography on silica gel (hexane–Et_2O, 4:1 with 1% triethylamine) to afford the product as a colourless solid.

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