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Construction of building-blocks for polyether synthesis using sequential catalytic ring-closing enyne and cross metathesis

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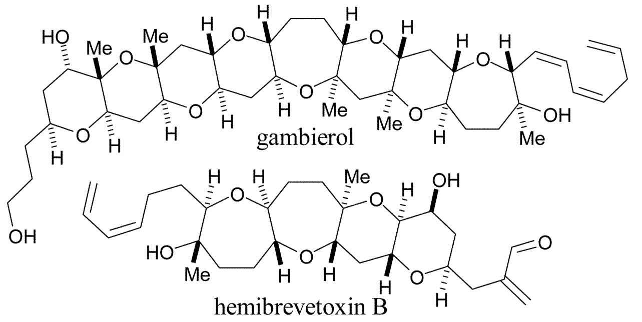
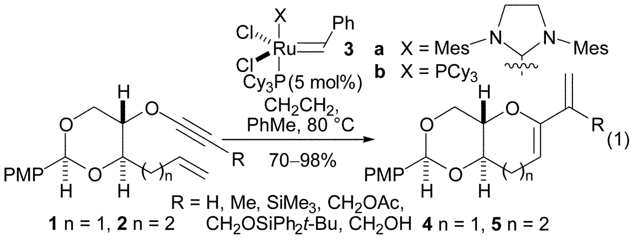
Received (in Cambridge, UK) 16th June 2004, Accepted 19th August 2004
First published as an Advance Article on the web 24th September 2004

Highly functionalised six- and seven-membered cyclic ethers bearing a variety of side chains have been synthesised using ring-closing enyne metathesis and subsequent cross metathesis of the intermediate diene; one-pot enyne and cross metathesis has also been accomplished, allowing ring construction and side chain introduction to be performed in a single operation.

Fused polycyclic ethers of marine origin are challenging and alluring synthetic targets.[1] Some members of this family of natural products, such as gambierol[2] and hemibrevetoxin B,[3] possess six- and seven-membered cyclic ethers exclusively, and rings of this size predominate in many of the others. Consequently, the rapid and stereoselective construction of highly functionalised six- and seven-membered cyclic ethers is a prerequisite for the efficient total synthesis of gambierol, hemibrevetoxin B and related marine natural products.



We recently reported that the carbohydrate-derived alkynyl ethers **1** and **2** undergo efficient ring-closing enyne metathesis,[4] mediated by the ruthenium complexes **3a**[5] and **3b**, to deliver the dienes **4** and **5** (eqn. (1)).[6] Although the metathesis reaction tolerates a wide variety of alkyne substituents (R) and the yields are usually excellent, the products possess a short side chain containing a vinyl group (R = H) or a 1,1-disubstituted alkene (R ≠ H). In subsequent work, we have attempted to functionalise the diene **4a** (R = H) by double hydroboration but the yield was low (<30%). We also investigated the cycloaddition reaction of the diene **4a** with singlet oxygen, as performed on related dienes by the groups of Martin and Nicolaou.[7] However, this approach was deemed to be inefficient because a modest yield of diastereomeric products is obtained and several steps are required to deliver functionality that is generated in a single operation by hydroboration.[7]



An attractive possible solution to the problem of selective functionalisation of the dienes **4** and **5** was to use cross metathesis to install a complex side chain immediately after ring-closing enyne metathesis of the alkynyl ethers **1** and **2**.[4] However, there are two potential problems with this sequence: competitive homo metathesis and ring-opening of the enyne metathesis products under the cross metathesis conditions. The latter issue is critical because generation of an alkylidene from the dienes **4** and **5** could result in ring-opening followed by cross metathesis. However, recent results from the groups of Grimaud and Lee suggested that it might be possible to perform successful cross metathesis on the dienes **4** and **5**.[8]

The cross metathesis reactions of the dienes **4a** and **5a** with a variety of alkenes mediated by the ruthenium complex **3a** were explored (eqn. (2), Table 1). Cross metathesis of the diene **4a** with allyl acetate to give the product **6a** was successful, but a superior yield was obtained when the diacetate of (*E*)-2-butene-1,4-diol was used as the coupling partner (entries 1 and 2, Table 1). Coupling of the diene **4a** with allyltrimethylsilane and the electron-deficient alkenes methyl vinyl ketone and methyl acrylate were also successful and delivered the products **6b–d** in excellent yield. However, the cross metathesis reactions of the diene **4a** with acrolein, allyl bromide and allyl chloride were unsuccessful even though the diene was largely consumed during the reaction (entries 6–8, Table 1).† The failure of these reactions is surprising because the successful cross metathesis of allylic halides with other alkenes is precedented.[9] Cross metathesis reactions of the seven-membered ether **5a** with allyl acetate, the diacetate of (*E*)-2-butene-1,4-diol, and methyl acrylate were also successful, affording the products **7a** and **7b** in excellent yield (entries 9–11, Table 1).

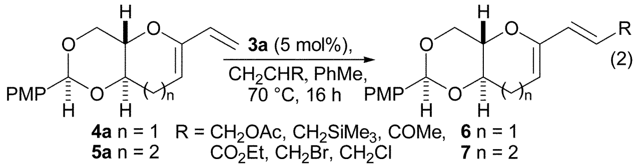


Table 1 Cross metathesis reactions of the dienes **4a** and **5a** with alkenes mediated by the ruthenium complex **3a** (eqn. (2))

Entry	Substrate	*n*	R	Product	Yield (%)[a]
1	**4a**	1	CH_2OAc	**6a**	91[b]
2	**4a**	1	CH_2OAc	**6a**	87
3	**4a**	1	CH_2SiMe_3	**6b**	78
4	**4a**	1	COMe	**6c**	79
5	**4a**	1	CO_2Et	**6d**	89
6	**4a**	1	CHO	**6e**	0
7	**4a**	1	CH_2Br	**6f**	0
8	**4a**	1	CH_2Cl	**6g**	0
9	**5a**	2	CH_2OAc	**7a**	84[b]
10	**5a**	2	CH_2OAc	**7a**	79
11	**5a**	2	CO_2Et	**7b**	91

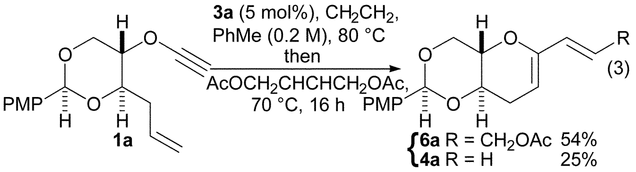
[a] Yield of isolated and purified product. [b] Reaction was performed using (*E*)-2-butene-1,4-diol diacetate instead of allyl acetate.

DOI: 10.1039/b409067e

The cross metathesis reactions of the substrates **4** and **5** bearing a 1,1-disubstituted alkene side chain (*i.e.* $R \neq H$) were investigated, but only starting material was recovered in each case. Similarly, attempted cross metathesis reactions of the vinylic substrates **4a** and **5a** with simple 1,1-disubstituted alkenes failed to deliver the expected products and substantial amounts of starting material were recovered in each case.

An attractive feature of our approach to diene functionalisation is the possibility of performing ring-closing enyne metathesis and diene cross metathesis in a single operation.[5] However, performing the reactions in a one-pot manner presents some difficulties because RCM is usually carried out using moderately dilute conditions and under an atmosphere of ethene, whereas cross metathesis is undertaken at higher concentrations with evaporative loss of a volatile alkene. Clearly, it is not possible to completely satisfy both sets of reaction conditions simultaneously.

A detailed exploration of the one-pot ring-closing and cross metathesis reaction of the alkynyl ether **1a** was undertaken (eqn. (3)). After considerable experimentation, it transpired that the one-pot reaction could be performed by effecting enyne metathesis at 80 °C in toluene under an atmosphere of ethene at a concentration of 0.2 M and then adding the diacetate of (*E*)-2-butene-1,4-diol and reacting at 70 °C whilst purging the atmosphere with argon.‡ Under these conditions, the cross-coupled product **6a** was obtained in 54% yield along with the RCM product **4a** in 25% yield. The concentration at which the reaction is performed was crucial to the success of the one-pot reaction: when the reaction was performed at concentrations of > 1 M the yield was reduced, and at lower concentrations (< 0.01 M) there was little cross metathesis and the intermediate diene **4a** was obtained. It was also crucial for ring-closing enyne metathesis to be complete prior to addition of the cross metathesis partner; mixing the alkynyl ether **1a** and the diacetate of (*E*)-2-butene-1,4-diol prior to addition of the ruthenium complex **3a** led to a complex mixture of products.

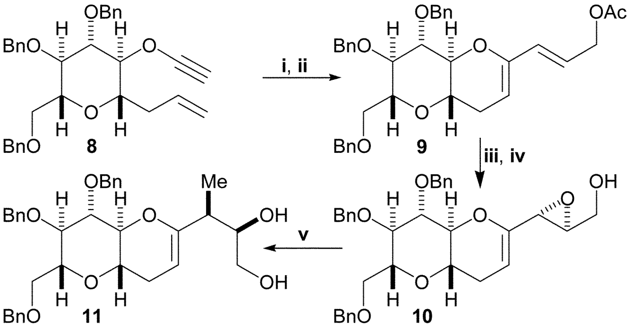


(3)

The successful replacement of the vinyl group of ring-closing enyne metathesis products **4** and **5** with elaborate side chains in a single operation is an important development. In addition to allowing rapid chain extension, cross metathesis allows selective functionalisation of the side chain to be performed without affecting the enol ether, which can be functionalised at a later stage. The side chain functional groups in the cyclic ethers **6** and **7** also permit the direct introduction of other substituents. For example, ring-closing enyne metathesis of the alkynyl ether **8** followed by cross metathesis of the resulting diene with the (*E*)-2-butene-1,4-diol diacetate afforded the bicyclic ether **9** in good yield (Scheme 1). Acetate cleavage and Sharpless asymmetric epoxidation of the resulting allylic alcohol led to stereoselective and regioselective side chain oxidation and delivered the epoxide **10**. A methyl substituent was then introduced by regioselective epoxide opening. The resulting diol **11** possesses a variety of functionality that can be elaborated independently.

In summary, we have shown that ring-closing enyne metathesis of alkynyl ethers followed by cross metathesis is a powerful sequence for the synthesis of six- and seven-membered cyclic ethers bearing complex side chain functionality. We have also demonstrated that the sequence can be performed in a one-pot fashion without isolation of the diene.

We thank the University of Nottingham and EPSRC (Grant No. GR/S15761/01) for financial support.



Scheme 1 *Reagents and conditions*: **i**, **3a** (5 mol%), CH_2CH_2, PhMe, 80 °C (82%); **ii**, **3a** (5 mol%), $AcOCH_2CHCHCH_2OAc$ (3 equiv.), PhMe, 80 °C (75%); **iii**, K_2CO_3, MeOH, rt (91%); **iv**, $Ti(O\textit{i}\text{-}Pr)_4$ (10 mol%), (+)-DET (15 mol%), *t*-BuOOH, CH_2Cl_2, −20 °C; **v**, MeLi, CuCN, Et_2O, $-60 \rightarrow 0$ °C (55% over 2 steps).

Notes and references

† Complex mixtures of polar products, arising from decomposition during the reaction or workup, were obtained.

‡ Experimental procedure for one-pot enyne metathesis and cross metathesis of alkynyl ether **1a** to give the diene **6a**: the ruthenium catalyst **3a** (15 mg, 18 μmol) was dissolved in dry toluene (1.8 mL) and ethene was passed through the solution for 5 min. The alkyne **1a** (100 mg, 0.365 mmol) dissolved in dry toluene (1.8 mL) was added to the solution of catalyst at room temperature under a static atmosphere of ethene. The solution was heated to 80 °C for 20 min before addition of (*E*)-2-butene-1,4-diol diacetate (190 mg, 1.10 mmol). The ethene atmosphere was then replaced by at atmosphere of argon and the reaction was stirred at 70 °C for 16 h. The volatiles were then removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (1:9 to 1:4 ether–hexane with 1% triethylamine) to give the coupled diene **6a** (68 mg, 54%) and the diene **4a** (25 mg, 25%) as colourless solids.

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