Pergamon

Tetrahedron Letters 39 (1998) 8321–8324

TETRAHEDRON LETTERS

Synthesis of Medium-sized Cyclic Allylic Ethers by Ring-closing Metathesis and Subsequent Elaboration to Sub-units Found in the Brevetoxins and Ciguatoxins

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Received 5 August 1998; accepted 28 August 1998

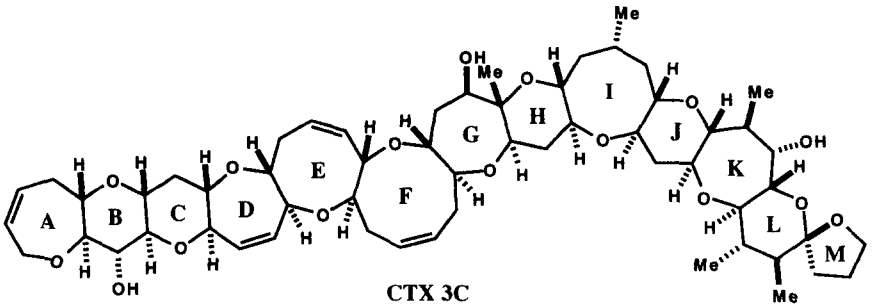
Abstract

Saturated and unsaturated seven- and eight-membered cyclic ethers of the type found in the brevetoxins and ciguatoxins have been prepared in enantiomerically pure form in 10 steps from a readily available chiral pool material. The key steps in this sequence are ring-closing metathesis of allylic ethers, and subsequent elaboration of the cyclic allylic ether products by stereoselective epoxide formation and ring-opening.

Keywords: ring-closing metathesis; brevetoxins; ciguatoxins; cyclic ethers

The brevetoxins and ciguatoxins are members of a burgeoning family of polycyclic ethers of marine origin.[1] Members of this family of natural products have captivated the interest of synthetic chemists due to their potent biological activities, fascinating molecular architectures and the inherent challenges,[2] especially with regard to ring synthesis and stereocontrol, that targets of such size and complexity present.[1]

All members of this family of natural products possess at least one medium-sized (7–9-membered) ring, and in most cases several medium-ring ethers are embedded within a single polycyclic array. An archetypal member of this class is the ciguatoxin CTX 3C which possesses a total of four seven-membered rings (A, D, G and K), two eight-membered rings (E and I) and a nine-membered ring (F).[3]

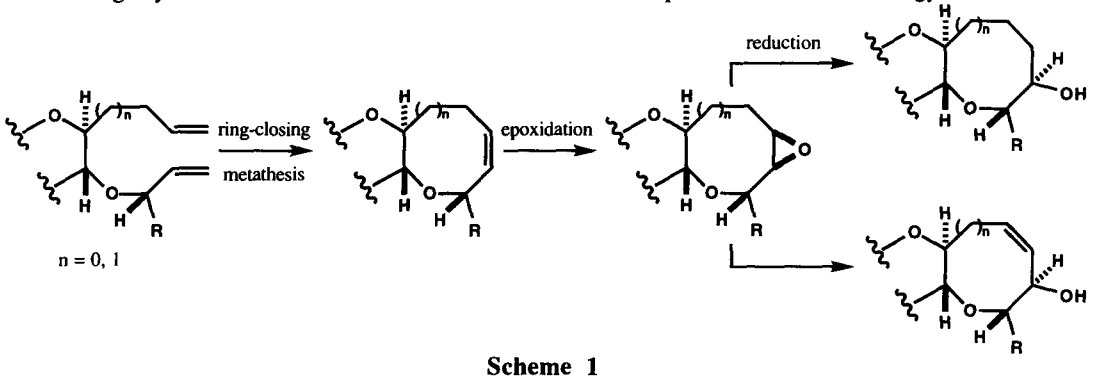


CTX 3C

Recently, we reported the preparation of highly functionalised enantiomerically pure *eight-* and *nine-*membered cyclic ethers in excellent yield by the ring-closing metathesis[4] of allylic ethers using the catalyst 2,6-(*i*-Pr)$_2$C$_6$H$_3$NMo[OC(CF$_3$)$_2$Me]$_2$CHCMe$_2$Ph (**1**).[5] However, these cyclic ethers lacked the oxygen functionality necessary for their further elaboration to sub-units found in the brevetoxins or ciguatoxins.[6] We now report the preparation of *seven-* and *eight-*membered cyclic allylic ethers, comparing the efficiency of the catalyst **1** to that of the more stable catalyst PhCHRu(PCy$_3$)$_2$Cl$_2$ (**2**),[7] and the subsequent elaboration of these metathesis products to saturated and unsaturated medium-ring ethers with the requisite functionality.

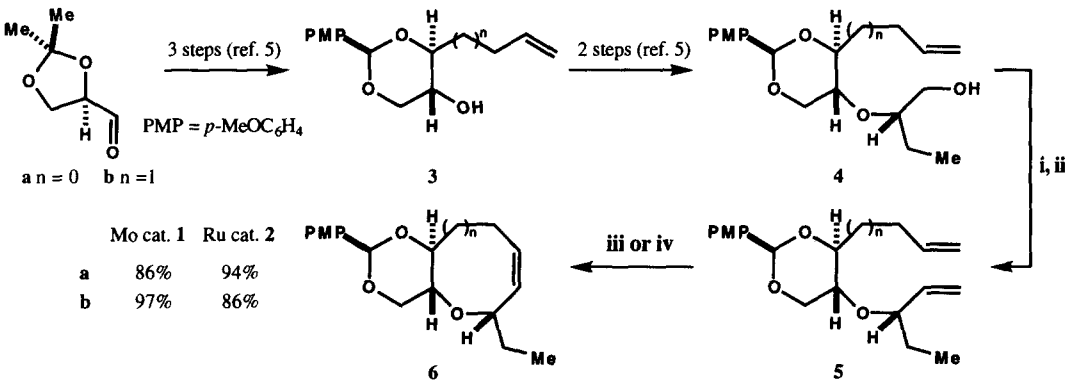
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01825-5

At the outset, we envisaged preparing the fully elaborated medium-sized cyclic ethers using the general strategy shown in **Scheme 1**. The key ring-forming step in this sequence was to involve ring-closing metathesis of suitably functionalised allylic ethers to give medium-sized (seven- or eight-membered) cyclic allylic ethers. The additional oxygen functionality required was then to be introduced by stereoselective epoxidation. Subsequent regioselective ring-opening of the epoxides with hydride would then provide the saturated medium-ring alcohols. Alternatively, "rearrangement" of the epoxides would provide the required medium-ring allylic alcohols. This *Letter* describes the successful implementation of our strategy.



Scheme 1

The precursors required for the study were prepared in an analogous fashion to those used in our previous work (**Scheme 2**).[5] The acetals **3a** and **3b** were prepared from (*R*)-2,3-*O*-isopropylidene glyceraldehyde by chelation controlled addition of allylmagnesium bromide or 3-butenylmagnesium bromide,[8,9] acetonide removal and reprotection of the resulting triol by acid-catalysed reaction with *p*-methoxybenzaldehyde dimethyl acetal.[5] The alcohols **4a** and **4b** were then obtained by alkylation of **3a** and **3b** with methyl 2-bromobutyrate and subsequent ester reduction using lithium aluminium hydride.[5] Conversion of the alcohols **4a** and **4b** into the dienes (**5a** and **5b**) required for the ring-closing metathesis reactions was accomplished by sequential Swern oxidation and Wittig methylenation (**Scheme 2**). Ring-closing metathesis reactions of the dienes **5a** and **5b** mediated by the complex 2,6-(*i*-Pr)$_2$C$_6$H$_3$NMo[OC(CF$_3$)$_2$Me]$_2$CHCMe$_2$Ph (**1**)[10] or the Grubbs complex PhCHRu(PCy$_3$)$_2$Cl$_2$ (**2**)[7] were then explored. High yields of the cyclic allylic ethers **6a** and **6b** were obtained using either catalyst, although the catalyst **1** usually delivered marginally higher yields (**Scheme 2**).



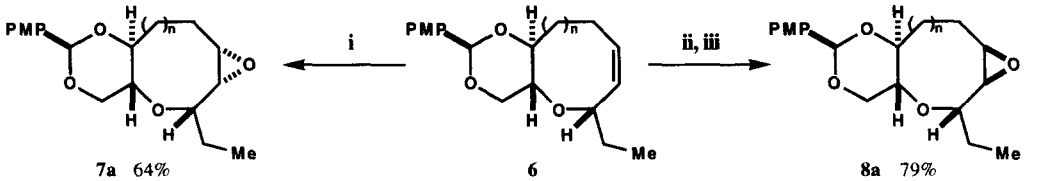
Reagents: **i** (COCl)$_2$ (2 equiv.), DMSO (4 equiv.), CH$_2$Cl$_2$, –60 °C, 1 h then Et$_3$N (11 equiv.), –60 °C→rt; **ii** [Ph$_3$PCH$_3$]$^+$Br$^-$ (1.5 equiv.), *n*-BuLi (1.3 equiv.), THF, rt, 12 h (**5a** 78% 2 steps, **5b** 59% 2 steps); **iii** 2,6-(*i*-Pr)$_2$C$_6$H$_3$N-Mo[OC(CF$_3$)$_2$Me]$_2$CHCMe$_2$Ph (**1**) (25–30 mol%), C$_6$H$_6$ (<0.02 M), rt (**5a**) or 60 °C (**5b**), 16–18 h; **iv** PhCHRu(PCy$_3$)$_2$Cl$_2$ (**2**) (10–20 mol%), C$_6$H$_6$ (**5a**) or CH$_2$Cl$_2$ (**5b**) (<0.01 M), rt, 12 h.

Scheme 2

Having prepared the seven- and eight-membered cyclic allylic ethers **6a** and **6b** in excellent yield, we then explored the elaboration of these compounds to give the fully functionalised saturated and unsaturated seven- and eight-membered cyclic ethers found in the brevetoxins and ciguatoxins (**Scheme 1**).

Simple epoxidation of both the allylic ethers **6a** and **6b** using *m*-CPBA proceeded in highly diastereoselective fashion and in reasonable yield to give a single crystalline epoxide in each case (**Scheme 3**).[11] Single crystal X-ray analysis revealed that we had obtained the epoxides **7a** and **7b**, which are diastereoisomers of the epoxides required.[11] Subsequent attempts to obtain the required products by performing the epoxidation reactions in other solvents and by using dimethyldioxirane as the oxidant did provide small amounts of the required epoxides in some cases, but the epoxides **7a** and **7b** always predominated.[12]

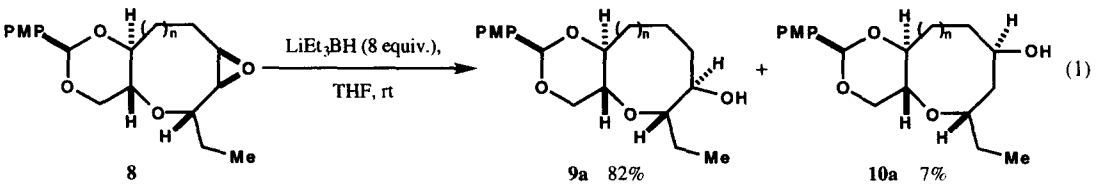
Ultimately, the inherent high π-facial selectivity encountered during the direct epoxidation procedure was exploited to our advantage, and we obtained the required products by sequential bromohydrin formation and base-promoted epoxide formation (**Scheme 3**).[13] Thus, reaction of the cyclic allylic ethers **6a** and **6b** with a slight excess of *N*-bromosuccinimide in aqueous DME in the dark, and treatment of the resulting bromohydrins with potassium *t*-butoxide afforded the required epoxides (**8a** and **8b**) diastereoselectively and in good yield.[13] In the case of the allylic ether **6a**, some of the epoxide **7b** was isolated along with the required epoxide **8b**.



Reagents: **i** *m*-CPBA, $CHCl_3$ (**6a**) or CH_2Cl_2 (**6b**), rt→reflux; **ii** *N*-Bromosuccinimide (1.1 equiv.), dark, DME-H_2O (3:1), rt, 12 h; **iii** *t*-BuOK (1.7 equiv.), *t*-BuOH, C_6H_6, rt, 5 h (**6a**) or *t*-BuOK (1.1 equiv.), *t*-BuOH, PhMe, rt, 1.25 h (**6b**).

Scheme 3

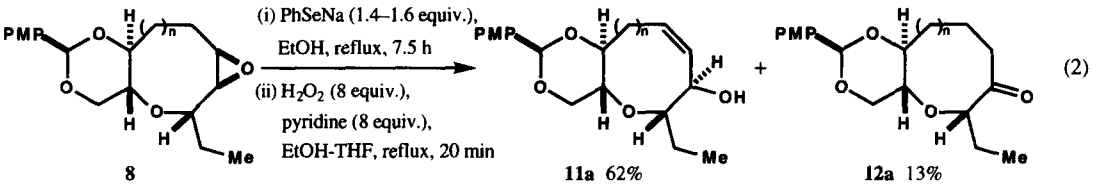
Regioselective ring-opening of the epoxides **8a** and **8b** with hydride was then studied (eq. 1). The choice of reducing agent was restricted due to the presence of the sensitive *p*-methoxybenzylidene acetal group in both substrates. Reduction of the epoxide **8a** with lithium aluminium hydride proceeded in good yield but with low regioselectivity to give the required alcohol **9a** in 57% yield and the regioisomeric compound **10a** in 31% yield. After considerable experimentation, we found that lithium triethylborohydride was a highly satisfactory reducing agent,[14] exhibiting good selectivity for reduction at least hindered position (γ to the oxygen of the medium-ring ether) (eq. 1). Reduction of the epoxide **8a** afforded the desired alcohol **9a** in 82% along with a small amount (7%) of the regioisomeric alcohol **10a**. When the same reduction reaction was performed on the epoxide **8b**, exclusive formation of the required alcohol **10b** was achieved in 91% yield.



(1)

Finally, we explored the conversion of the epoxides **8a** and **8b** into the allylic alcohols **11a** and **11b** (eq. 2). Attempts to accomplish this transformation directly by base-promoted rearrangement of the epoxides were not successful, and complex mixtures of products were obtained instead of the required allylic alcohols.[15] However, we were able to perform the desired transformation using Sharpless' procedure for the conversion of epoxides to allylic alcohols.[16] Thus, selective nucleophilic opening of each epoxide at the least hindered position

was achieved using sodium phenylselenide generated *in situ* by the reaction of diphenyl diselenide with sodium borohydride (eq. 2). Subsequent treatment of the unpurified hydroxy selenides with excess hydrogen peroxide in the presence of pyridine, followed by immediate selenoxide elimination gave each of the required allylic alcohols (**11a** and **11b**). The alcohol **11a** was a crystalline solid, and the relative stereochemistry of this product was confirmed by X-ray crystallography. As anticipated, selenoxide elimination was directed away from the hydroxyl group. However, in the case of epoxide **8a**, some of the ketone **12a**, resulting from elimination toward the hydroxyl group and subsequent enol-keto tautomerism, was isolated from the reaction.



(2)

8 a n = 0 b n = 1

11a 62% **11b** 61% **12a** 13% **12b** 0%

The synthesis of enantiomerically pure saturated and unsaturated seven- and eight-membered cyclic ethers was achieved in 10 steps from chiral pool derived aldehyde (*R*)-2,3-*O*-isopropylidene glyceraldehyde. The sequences of reactions described above constitute a general and efficient approach to the construction of medium-sized cyclic ether sub-units of the type found in the brevetoxins and ciguatoxins, and are also suitable for the preparation of the core structures of many of the *Laurencia* metabolites.[17]

Acknowledgements: The EPSRC is gratefully acknowledged for funding this work through the award of a postdoctoral fellowship, and the European Commission is gratefully acknowledged for the award of a Marie-Curie Fellowship (to O.H.) as part of the TMR Programme. We thank Dr. A. J. Blake, Dr. W.-S. Li and Dr. P. Cooke for performing X-ray crystallographic analysis on the compounds **7a**, **7b** and **11a**.

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