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Biomimetic Cyclisation of Prebrevetoxin Polyepoxide Models

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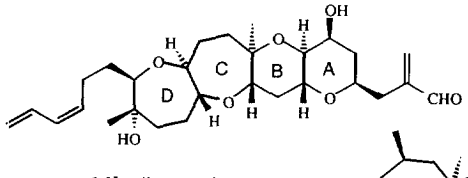
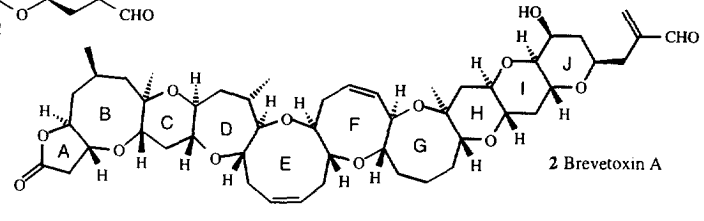
Abstract. (*E*)-1,3-Dihydroxyhex-4-ene and (*E*)-1,3-dihydroxy-4-methylhex-4-ene undergo epoxidation with peracetic acid and *in situ* cyclisation to give a mixture of tetrahydro-furans and -pyrans, whereas comparable compounds lacking the allylic hydroxyl group give predominantly or exclusively tetrahydrofurans. These reactions model the first cyclisation of prebrevetoxin polyepoxides and demonstrate the regio-directing effect of the hydroxy group adjacent to the epoxide.

The brevetoxins consist of three main ring types exemplified by hemibrevetoxin[1] **1**, brevetoxin-A[2] **2** (Scheme 1) and brevetoxin-B[3] **4a** (Scheme 2). Brevetoxin C[4] **4c**, GB-3[5] **4b**, GB-5 **4f**, GB-6[6] **4g** have the same carbon skeleton as brevetoxin B **4a**, but with different side chains.[7] Recently three new brevetoxins have been isolated from New Zealand cockles, *Austrovenus stutchburyi* and greenshell mussels, *Perna canaliculus*. Brevetoxins B1[8] **4d** and B2[9] **4e** also have the same carbon skeleton as brevetoxin B, but different side chains at C-39, whereas brevetoxin B3 has a terminal carboxylic acid group and the D-ring is cleaved.[10]

All of the brevetoxins share the re-occurring motif of *trans*-fused ether rings, but have different carbon skeletons. However, a terminal perhydrobis-pyran bearing a side chain and a hydroxyl group is a conserved feature in all brevetoxins. This observation gains further importance in the context of the proposal, that the final biosynthetic step is an epoxide cascade, initiated by a hydroxyl group (eg at C-39 in prebrevetoxin polyepoxide **3a**, Scheme 2).[11] In contradiction to this proposal, 4,5-epoxy-alcohols normally undergo cyclisation to give tetrahydro-furans rather than -pyrans.[12] However, the C-37 hydroxyl group is ideally placed to influence the regiochemistry of the first epoxide cleavage/tetrahydropyran formation reaction. We envisaged that it might destabilise carbonium character at the adjacent carbon and hence promote tetrahydropyran formation.[13] In this *letter* we describe three model reactions which test this proposal.



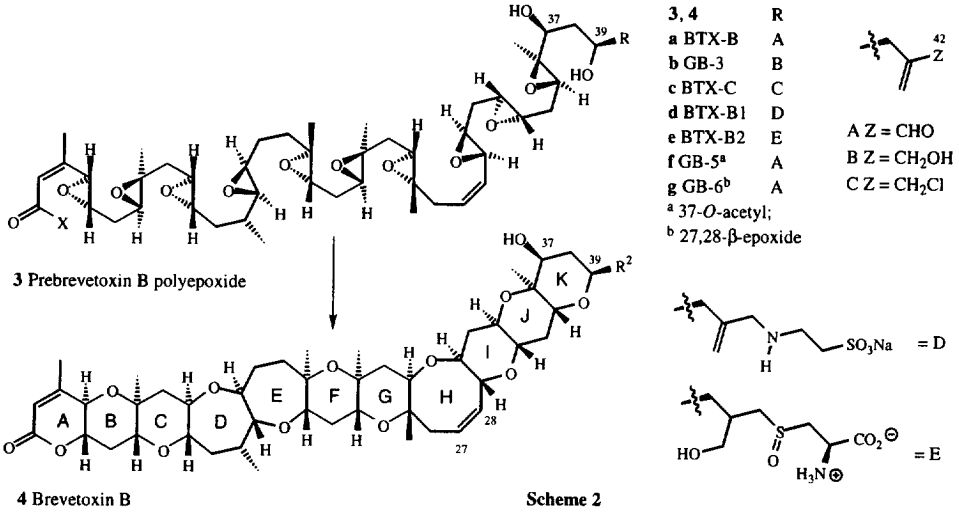
1 Hemibrevetoxin



2 Brevetoxin A

Scheme 1

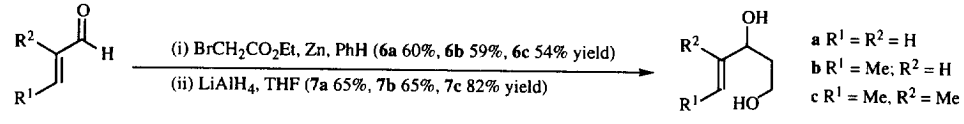
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00376-7



Scheme 2

Our approach to the synthesis of model compounds was tempered by the knowledge that 4,5-epoxy-alcohols cyclise readily and that protected derivatives have the potential to cyclise during the removal of the protecting groups. We therefore elected to epoxidise the corresponding alkenes using peracetic acid in chloroform and cyclise *in situ* catalysed by acetic acid. All biomimetic reactions are open to the criticism that the conditions can never truly mimic those of an enzyme active site. Nevertheless the pH is realistic for an epoxide hydrolase active site, less objectionable than the use of strong acids and bases and untainted by coordination phenomena (for example due to titanium alkoxides).

The precursor alkenes **7** were prepared by the Reformatsky reaction of ethyl bromoacetate and the requisite commercially available aldehydes **5** (Scheme 3). The esters **6** so formed were reduced with lithium aluminium hydride[14] using silica gel and the minimum amount of water to decompose the alkoxides in order to minimise loses of the water soluble diols.[15]

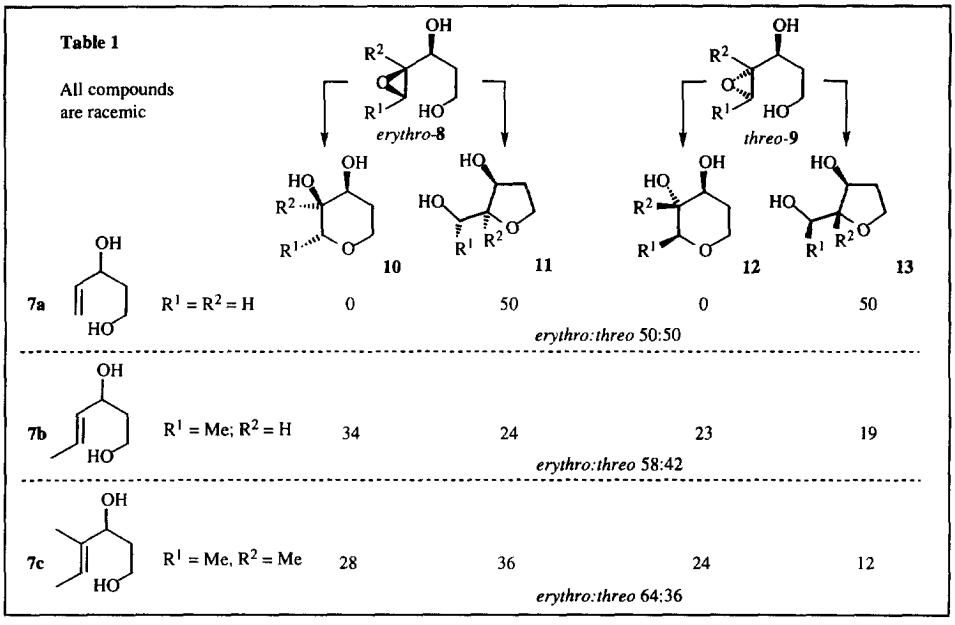


5 Scheme 3 7

Epoxidation of the "unsubstituted" alkene **7a** required 24h and gave exclusively the tetrahydrofurans **11a**[16], **13a** which were identified as the diacetate derivatives. The ^{1}H-NMR spectrum of the crude reaction mixture showed no trace of the tetrahydropyrans **10a**, **12a** and reaction of an aliquot with periodate caused no change in the components observed by TLC, indicating the absence of 1,2-diols **10a**, **12a**. This result is comparable with the mCPBA epoxidation/cyclisation of 4-penten-1-ol which gives a 96:4 ratio of tetrahydro-furan:-pyran products.[17] The absence of tetrahydropyrans can be attributed to the greater carbonium character at C-4 relative to C-5 in the protonated epoxide, due to the greater stabilisation of the former.

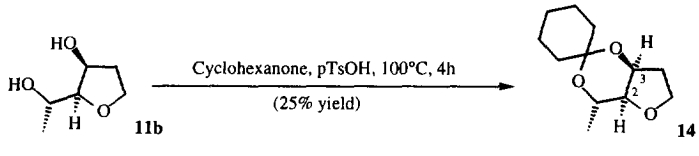
Table 1

All compounds are racemic



Reagents and conditions: $CHCl_3$, NaOAc (0.1 equiv.), 0°C, AcO_2H (35% solution in AcOH, 2 equiv. **7a**, 1.1 equiv. **7b**, **7c**), 3-24h.

Alkene **7b**, which is a model for prehemibrevetoxin and prebrevetoxin A polyepoxides, underwent epoxidation/cyclisation in 12hrs to give a mixture of four components which were separated by column chromatography. The tetrahydopyrans **10b**, **12b** were identified by comparison with authentic materials produced by unambiguous syntheses from tri-*O*-acetyl-D-glucal.[18] The tetrahydrofurans **11b**, **13b** gave complex ^{1}H-NMR spectra due to poor signal dispersion. The more abundant component gave a cyclohexylidene ketal derivative **14** ($^3J_{2,3}$ = 4.4Hz) and hence was assigned as the *cis*-isomer **11b**, whereas the less abundant component **13b** ($^3J_{2,3}$ = 3Hz) was recovered unchanged after several days under the same conditions.



Alkene **7c** which is a model for prebrevetoxin B polyepoxide **3**, underwent epoxidation/cyclisation in 3 hrs to give a mixture of four products. The products from the *erythro*- and *threo*-epoxides were readily separated by column chromatography, but the mixtures of tetrahydro-furans and -pyrans so formed were inseparable. Fortunately the ^{1}H-NMR spectra were sufficiently similar to those of **10b-13b** that assignments could be made using the mixtures.

If the cyclisations are assumed to proceed with inversion of configuration at the centres undergoing nucleophilic attack, the ratios **10+11**:**12+13** reflect the *erythro:threo* selectivity of the initial epoxidation of the alkenes **7a-c**. The values obtained; **a** 50:50, **b** 58:42, **c** 64:36 are similar to those obtained for

compounds lacking the terminal hydroxyl group (typically 40-50:60-50).[19]

The ratios of the products **9-13** cannot be explained by a single model. It was anticipated that the preference for tetrahydropyran formation would be greater for the *erythro*-epoxides **8b, 8c** than for the *threo*-epoxides **9b, 9c**, because the former have the same relative stereochemistry as the prebrevetoxin epoxides. The **b** series compounds marginally show this effect 60:40 (**10b**:**11b**) *vs* 55:45 (**12b**:**13b**), whereas the *erythro*-epoxide **8c** gives marginally less tetrahydro-pyran than -furan 45:55 (**10c**:**11c**) and the *threo*-epoxide **9c** shows the strongest preference observed for tetrahydro-pyran over -furan formation, 66:33 (**12c**:**13c**). In fact contrary to expectations, only the *threo*-epoxides **9b, 9c** consistently give more tetrahydro-pyran than -furan. Nevertheless the epoxidation/cyclisations of the alkenes **7b, 7c** show an increased preference for tetrahydropyran ring formation, relative to comparable compounds which lack the allylic hydroxyl group,[20,21] although the effect is not synthetically decisive.

One possible speculation, is that the hydroxyl group adjacent to the epoxide is esterified to the enzyme which enhances the electron withdrawing effect and hence increases the regioselectivity in favour of the tetrahydropyrans. This possibility is currently under investigation.

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18. The tetrahydropyrans **10b**, **12b** can be regarded as 1,2,6-trideoxyhexoses. Hydrogenation of tri-*O*-acetyl-D-glucal and de-esterification gives a triol. The 6-hydroxyl group of the triol was tosylated, converted to the iodide and reduced with Bu_3SnH to give the *trans*-diastereoisomer *ent*-**12b**. The triol was also converted to the 4,6-*O*-benzylidene derivative and the 3-hydroxyl group inverted by a Mitsunobu reaction. Hydrogenolysis of the benzylidene group, de-esterification, selective tosylation of the 6-hydroxyl group and one pot displacement/reduction by NaI/Bu_3SnH gave the *cis*-diastereoisomer **10b**. Full details will be reported elsewhere.
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