The stereochemical course of bromoetherification of enynes†

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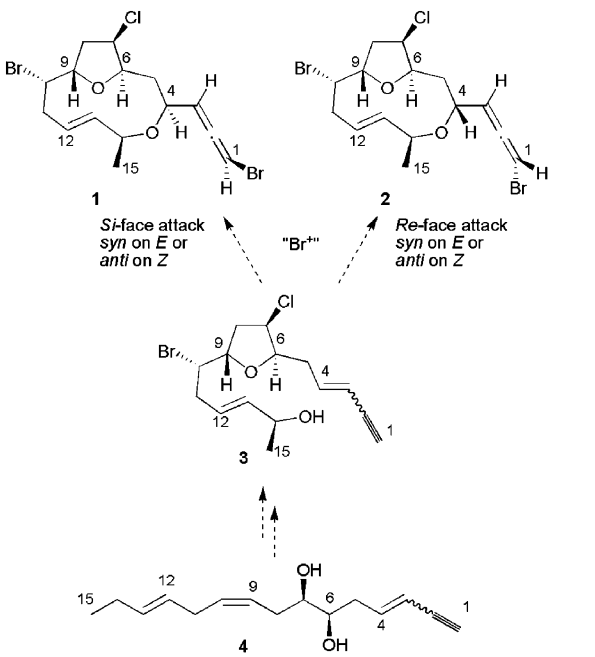
Enynes undergo stereoselective *syn* intramolecular bromoetherification; the stereochemical course of the reaction was elucidated by X-ray crystallographic studies and by stereospecific synthesis of authentic bromoallenes.

The bromoallene motif occurs widely in the halogenated C_{15} acetogenic metabolites isolated from *Laurencia* species;[1] obtusallenes II (**1**)[2] and IV (**2**)[3] are representative. We have recently proposed a biosynthetic hypothesis concerning the formation of the obtusallenes where their bromoallene unit may be formed by an electrophilic macrobromoetherification of enyne **3** (Scheme 1).[4] Inspection of the obtusallene II and IV structures reveal them to have identical tetrahydrofuran cores, but are epimeric at both C_4 and with respect to the chiral bromoallene. This analysis suggests that they therefore arise from the same enyne precursor, that nucleophilic attack of the alcohol can be on either the *Si* or *Re* face of the enyne at C_4, and that the *bromoetherification is stereospecific*. However, the overall stereochemical outcome of the bromoetherification will also be controlled by the original double bond geometry of the enyne. For instance, the required stereochemistries of the obtusallene bromoallenes could arise either by *syn* addition to an *E*-enyne or *anti* addition to a *Z*-enyne. Biomimetic intramolecular bromoetherification of enynes has previously been demonstrated for other members of the wider natural product family, to give mixtures of diastereomeric bromoallenes, where pre-existing stereocentres may affect the diastereoselectivity.[5] In addition, laureddiol **4**, which is the generally accepted biosynthetic precursor of the entire family has been isolated with both *E* and *Z* enyne configurations.[6] We now show that in the absence of any other perturbing chiral centres, the intramolecular bromoetherification of enynes is stereoselective, and proceeds *via syn* addition.

Substrates *E*-enyne **5** and *Z*-enyne **6** were selected to investigate the stereochemical course of bromoetherification. It was expected that if the bromoetherification was stereospecific, each substrate would give different bromoallene diastereomers **7a** or **7b** on bromoetherification. Thus, if the bromoetherification proved to occur in a *syn* fashion, *E*-enyne **5** would give bromoallene **7a**, the *Z*-enyne **6** giving diastereomeric bromoallene **7b**. If however, the bromoetherification is *anti* specific, then the *E*-enyne would give rise to **7b**, and the *Z*-enyne would give **7a** (Scheme 2).

E-Enyne **5** and *Z*-enyne **6** were prepared starting from silyl ether **8**[7] (Scheme 3). PCC mediated oxidation gave aldehyde **9**.[8] *E*-Selective enyne formation with the ylide derived from phosphonium salt **10**[9] and NaHMDS gave protected enyne **11**. Double deprotection with TBAF gave the *E*-enyne **5**. Alternatively, silyl ether **8** was converted first into iodide **12**,[10] and then into phosphonium salt **13**[11] (Scheme 4). Wittig reaction with propynal **14**[12] gave TMS-enyne **15** as an inseparable 1.6 : 1 mixture of *Z* : *E* geometric isomers. TBAF deprotection as before gave a 1.6 : 1 mixture of *Z*- and *E*-enynes **6** and **5**, respectively.

Bromoetherification of **5** proceeded smoothly with NBS (100% conversion, 4 h, $CDCl_3$, −40 °C to r.t.) to give a 6 : 1 mixture of diastereomeric bromoallenes **7**.‡ Bromoetherification of **6** under identical conditions gave the same diastereomeric allenes **7** but in a reversed 1 : 7 ratio.§ These experiments



Scheme 1 Postulated bromoallene formation of obtusallenes II and IV.

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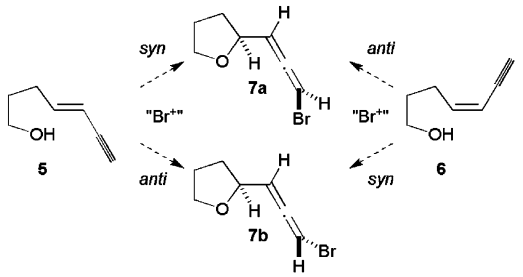
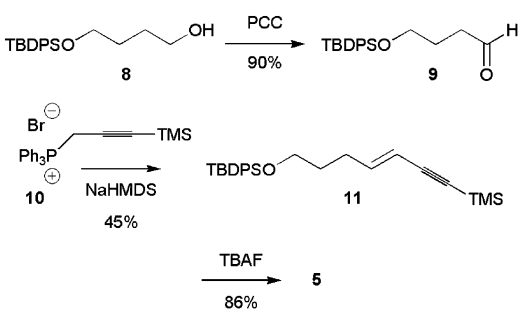
† Electronic supplementary information (ESI) available: Notes ‡,§,¶,††,**,¶¶,‡‡,***, full experimental details for the preparation of compounds **11**, **5**, **15**, **6**, **16–17**, **7a**, **19–23**, **25–28** and X-ray crystallographic details for **24**. CCDC 625183. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b800054a



Scheme 2 Stereospecific bromoetherifications.

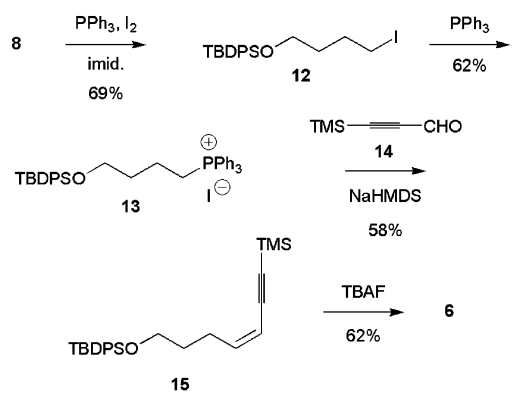


Scheme 3 Synthesis of *E*-enyne **5**.

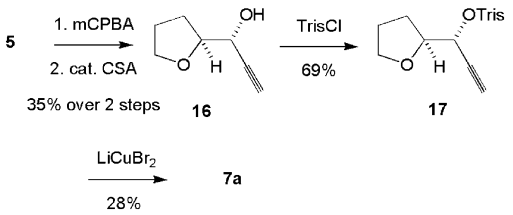
demonstrate that the course of bromoetherification of enynes is essentially stereospecific.

To assign the relative stereochemistry of the bromoallene products and hence the mode—*syn vs. anti*—of addition, authentic bromoallene **7a** was prepared by a stereospecific route from *E*-enyne **5** (Scheme 5). *Syn*-epoxidation of **5**, followed by acid-catalysed stereospecific ring-opening of the epoxide gave known alcohol **16**.[13] Activation of the alcohol as the trisylate **17**[14] and stereospecific *anti* S_N2'-bromoallene formation[15] gave **7a** as expected.[16] This proved to be identical to the major product from bromoetherification of **5** showing that bromoetherification proceeds with *syn* selectivity, and also allows assignment of bromoallene **7b** as the major diastereoisomer resulting from the cyclisation of enyne **6** (also by *syn* addition).

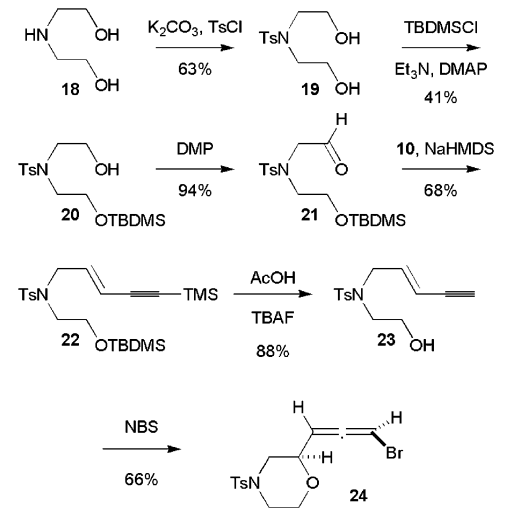
To further unambiguously elucidate the stereochemical course of bromoetherification of enynes we determined to prepare a substrate that would give a crystalline bromoallene on cyclisation. Accordingly, diethanolamine **18** was *N*-tosylated to give tosyldiol **19** (Scheme 6).[17] Monoalcohol protection to **20**, followed by DMP[18] oxidation to aldehyde **21** and *E*-selective Wittig reaction using phosphonium salt **10** gave protected enyne **22**.¶ Deprotection with acetic acid-buffered TBAF gave *E*-enyne **23**.†† Enyne **23** cyclised smoothly on treatment with NBS, to give bromoallene **24** as a 4.5 : 1 mixture of diastereomers.¶¶ Bromoallene derivative **24**** proved to be crystalline and could be analysed by single-crystal X-ray crystallography. The two diastereoisomers co-crystallised in a 5.7 : 1 ratio and inspection of the structure of the major diastereoisomer revealed that the bromoetherification had occurred by *syn* addition.‡‡ Thus the *syn* cyclisation



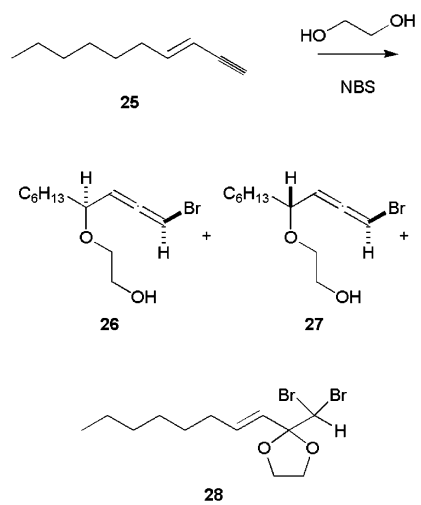
Scheme 4 Synthesis of *Z*-enyne **6**.



Scheme 5 Stereospecific synthesis of bromoallene **7a**.



Scheme 6 Synthesis and cyclisation of *E*-enyne **23**.



Scheme 7 Intermolecular bromoetherification.

pathway occurring by a 5-*exo*-mode is also followed in a 6-*exo*-mode

We have also explored the intermolecular bromoetherification reaction of an unfunctionalised enyne **25** with ethylene glycol as a representative alcohol. To the best of our knowledge this intermolecular reaction is unprecedented in the literature. In preliminary experiments in dichloromethane using 10 equivalents of added diol, although characteristic bromoallene signals were observed in the ^{1}H NMR spectrum, a complex mixture of products were obtained, presumably as the result of competitive intermolecular attack of a second enyne on an incipient bromonium ion. In contrast using ethylene glycol as the solvent (300 equivalents) gave rise to bromoetherification with two diastereomeric bromoallenes **26** and **27***** isolated in 7 and 6% yield, respectively after column chromatography (Scheme 7). A dibrominated adduct **28** (10%) was also isolated that must arise by initial attack of the alcohol directly at the brominated alkyne of the enyne. The relative ratio of **26** : **27** was essentially 1 : 1 by inspection of the ^{1}H NMR spectrum of the crude product, showing that the intermolecular bromoetherification reaction is not stereoselective under these conditions.

In conclusion, we have shown that an unperturbed intramolecular bromoetherification of an enyne proceeds by stereoselective *syn* addition. The inherent stereoselectivity is higher than those observed to date in the cyclisation of enynes to bromoallenes in more complex systems with pre-existing stereocentres.[5] Mechanistically we propose that a bromonium ion is formed on the alkyne followed by nucleophilic attack of the alcohol under stereoelectronic control. This is consistent with the stereochemical outcome (*syn*) of the overall addition of Br_2 across a 1,3-diene where the participating orbital array is essentially identical.[19] The above findings represent fundamental stereochemical information with respect to electrophilic 1,4-addition across an enyne. Moreover, it should guide the choice of enyne geometry required in the synthesis of natural products from *Laurencia* species. In particular it allows us to target an *E*-enyne for the synthesis of obtusallenes II and IV.[20,21]

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