

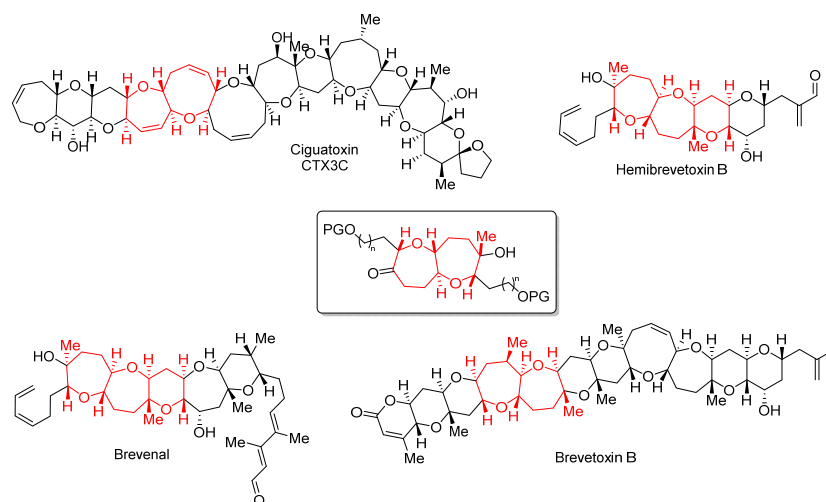
CENTROSYMMETRIC APPROACH TOWARDS THE SYNTHESIS OF FUSED POLYCYCLIC ETHER NATURAL PRODUCTS

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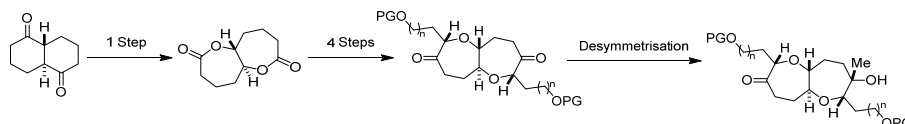
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Fused polycyclic ether natural products are found in marine dinoflagellates and higher organisms which feed on algae.¹ Many of these natural products are potent neurotoxins that are responsible for human poisoning episodes; however, a small selection of these compounds are potential lead compounds for the development of new drugs.² For example, brevetal can be used to treat the effects that arise due to exposure to the brevetoxins.³ The formation of fused polycyclic ethers has posed many a challenge to researchers, in terms of ring size, stereochemistry and step count.⁴

We are developing a novel and highly efficient route towards the fused polycyclic ether systems that allows rings to be constructed bidirectionally by exploiting both the apparent and hidden symmetry embedded in the natural products. This approach will allow complex bicyclic systems to be prepared in 4-8 steps, therefore significantly reducing the length of routes towards many natural products.



The strategy involves the synthesis of achiral centrosymmetric bicyclic systems from bicyclo[4.4.0]decanes, which undergo ring expansion to the desired *trans*-7,7-membered cyclic ethers. Synthesis of the centrosymmetric dione from the bis-lactone requires only 4 steps. Desymmetrisation of the centrosymmetric dione affords the key intermediate that will be used to prepare a wide variety of other bicyclic systems allowing access to hemibrevetoxin B and many other natural products.



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[3] H. Fuwa, M. Ebine, A. J. Bourdelais, D. G. Baden and M. Sasaki, *J. Am. Chem. Soc.*, 2006, 128, 16989–16999.

[4] K. C. Nicolaou and R. J. Aversa, *Isr. J. Chem.*, 2011, 51, 359–377.