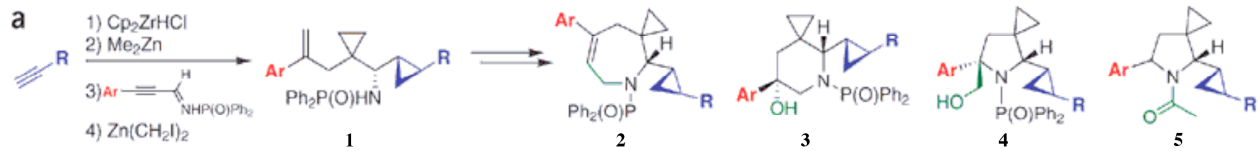
Diversity Oriented Synthesis (DOS)

ARB Problem Questions November 2010

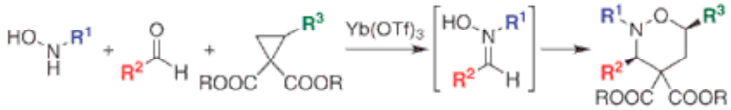
Diversity oriented synthesis expanded from the area of combinatorial chemistry that first emerged in the 1980s. Limitations to the variety of reactions and products seen in combinatorial chemistry resulted in the emergence of research into using the linear nature of combinatorial chemistry to synthesise a large range of chemically diverse small molecule libraries often exploring areas of chemical space not investigated by big pharma due to complex stereochemistry or complex polycyclic nature of some compounds.

These questions will explore some of the chemistry used in DOS approaches to this problem.

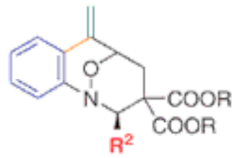
1 The synthetic scheme below highlights the work of Peter Wipf in the DOS of a series of azaspirocycly compounds **2-5**. Provide a mechanism for synthesis dicyclopropylmethyl amide **1** and reagents and a mechanism for the consequent conversion of **1** to spirocycles **2-5** (a 2 step procedure from **1** is used in each case).



2(a) Kerr *et al.* described the synthesis densely functionalised tetrahydro-1,2-oxazines from nitrones and cyclopropanes. Give the mechanism for the synthesis of **6** from the LHS starting materials.

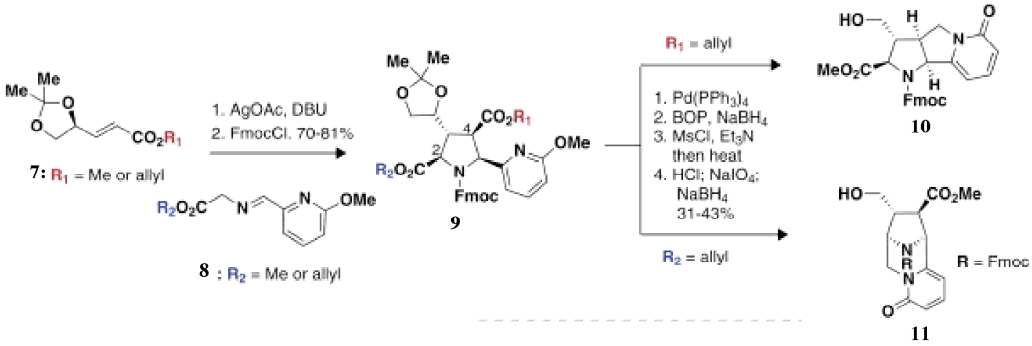


(b) Use of suitably substituted analogues of starting materials gave the ability for synthesis of the skeleton of natural product **FR-900482**. Give the required substituents and propose reagents required for this transformation.

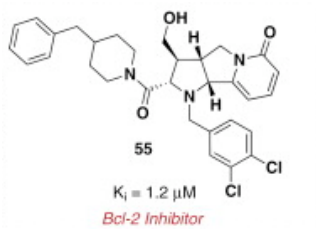


FR-900482

3(a) Use of orthogonal protecting groups allowed Marcaurelle *et al.* to selectively synthesise bicyclic and triciclic alkaloid type cores **10** and **11** through a 4-step procedure from **9**. Give mechanisms for the synthesis of **10** and **11.**

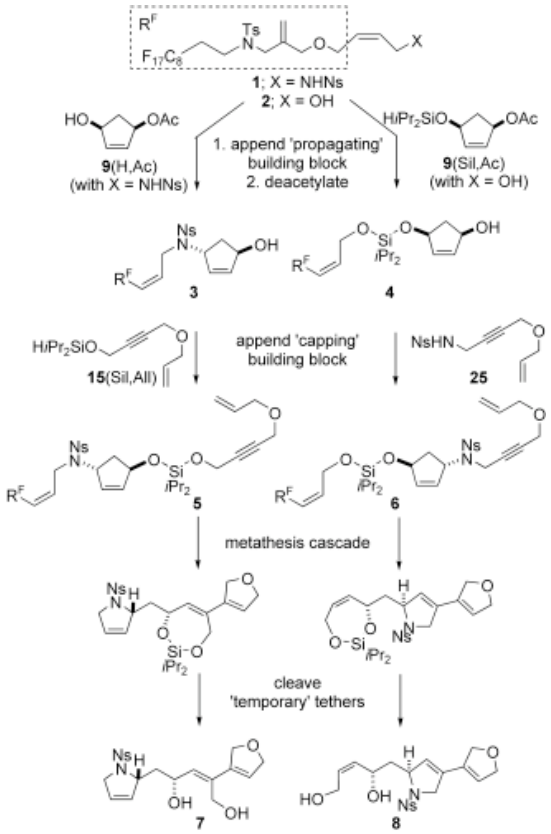


(b) Bicyclic compound **10** was loaded on to the solid phase and used to create a library of ~15000 compounds. One of these compounds, **55**, was identified to be a potent Bcl-2 inhibitor. Described a solid phase synthetic procedure to produce **55** from **10**.



In 2008 Stuart Scheiber coined the term ‘build-couple-pair’ (B-C-P) as a rational approach to DOS.

4. In the same year Nelson *et al.* created 80 structurally distinct scaffolds from 25 pre synthesised ‘parent scaffolds’ through this B-C-P approach.



Give reagents and mechanisms for each step of this example B-C-P pathway.

THE END