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Planning Organic Syntheses: Tactics, Strategy and Control

Introduction: The Purpose of this Workbook

You have made a good start in your investigation of more advanced organic synthesis by, we suppose, reading the textbook *Organic Synthesis: Strategy and Control*. A lot can be learnt from reading but, to gain a real understanding of a subject, more involvement is needed. The workbook gives you more examples of the chemistry discussed in the main text to expand your experience. More importantly, it also offers the opportunity to put your understanding to the test by providing sets of problems with worked answers. Each chapter contains further details of, and recent developments in, the chemistry discussed in the chapter. There is little to add to this short chapter, however.

Other Literature on Organic Synthesis

The list of general references gives you many valuable resources. We would like to draw your attention here to other ways of looking at organic synthesis. Many organic chemists think that the synthesis of natural products is the highest goal for chemistry. A masterly and entertaining account[1] of the synthesis of the 'CP molecules' – naturally occurring cholesterol-lowering fungal metabolites – uses the analogy of Theseus hunting the minotaur target molecule through the labyrinth (organic synthesis).

Sharpless[2] has put forward the challenging and interesting idea that organic synthesis, particularly the discovery of new drugs, should focus not on natural products but on molecules that are easy to make. He uses an estimate by Guida that there are about 10^{62} potential 'reasonable' drug molecules and there are not enough atoms in the universe to make even one molecule of each. Random searching is doomed. Sharpless proposed a new type of chemistry – 'click' chemistry – that uses only kinetically controlled and very favourable reactions of alkenes so that the amount of material from each step increases rather than the typical arithmetic decrease in so many natural product syntheses. This idea has many adherents.

Another challenging article[3] on the success or otherwise of organic synthesis questions the philosophy behind much of the synthetic work of the 1990s – the title 'Dead Ends and Detours en Route to Total Syntheses' reveals the line taken by the authors.

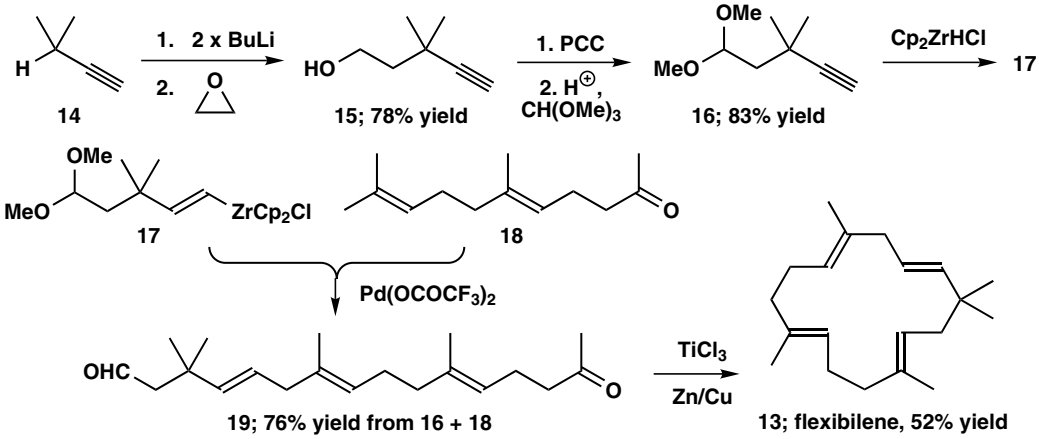
Workbook for Organic Synthesis: Strategy and Control Paul Wyatt and Stuart Warren

The Synthesis of Fostriecin

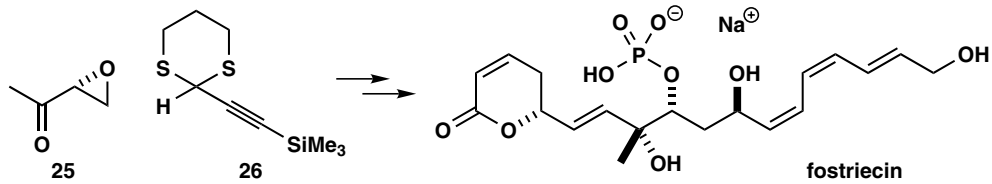
This interesting molecule has continued to attract attention and you can read about other syntheses.[4]

Examples of Problems

In our minds we have categorised problems as 'simple', 'tricky' or 'taxing'. This is partly to provide problems of progressive difficulty and partly to set your mind at rest when you find a problem too difficult. Here are some examples to give you the idea:
Simple: Identify which atom in the final intermediate **19** becomes which atom in flexibilene TM **13**. Suggest mechanisms for the reactions giving **15** and **16**.

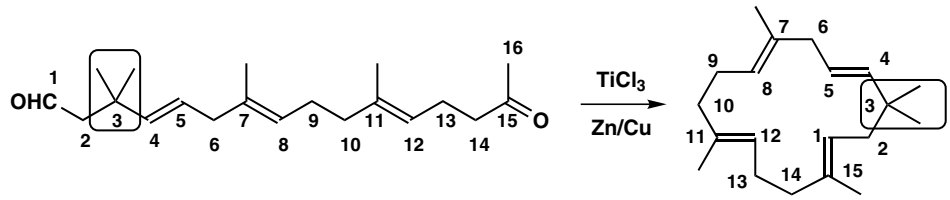


Tricky: Which reactions control the stereochemistry of each double bond in flexibilene TM **13**?
Taxing: Suggest how compound **26** might be combined with compound **25** in the synthesis of fostriecin. What problem(s) of selectivity do you foresee?



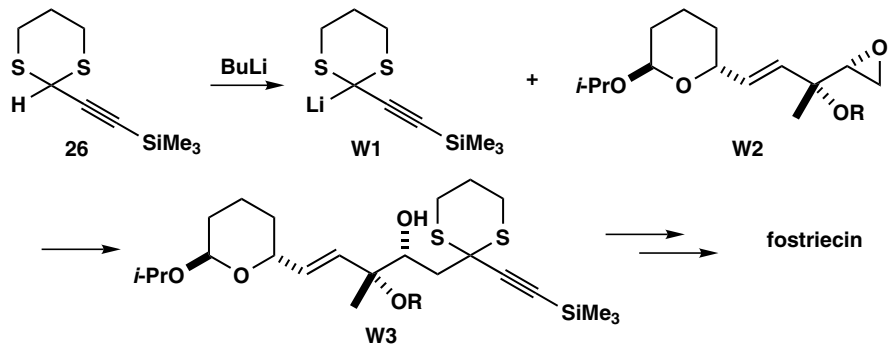
Examples of Answers

These will usually give full details and literature references or at least enough, as here, to put you on the right track.
Simple: The best technique is to number (arbitrarily) the atoms is either the starting material or the product. This technique is also helpful in solving complicated mechanistic problems. Here the linear starting material is most easily numbered. Inspection of flexibilene makes atom 3 easy to identify. The counting round to the nearer alkene (or the nearer methyl group) reveals which way round you should number flexibilene. The new alkene is evidently between C-1 and C-16.



Tricky: Two alkenes (C-11/C-12 and C-8/C-9) are already present in the starting material **18**. One (C-4/C-5) first appears in **19** but is really made by the hydrozirconation reaction giving **17**. As you will see in chapter 16, such reactions occur with retention of configuration. The final alkene is formed stereoselectively in the McMurry cyclisation of **19**. Notice that the 15-membered ring can accommodate *four E*-alkenes – and prefers to do so. This is a bit surprising as one *E*-alkene becomes possible only in an eight-membered ring.

Taxing: You might have made several different suggestions here and it is important for you to realise at this early stage that *there is no 'correct' answer to a synthesis question*. After all, there are many syntheses of fostriecin and only this one couples these fragments. The most obvious thing is to make the lithium derivative of the dithian **26** and combine it with the epoxide or the ketone in **25**. The selectivity problem is which reaction is preferred. Chavez and Jacobsen[5] did make the lithium derivative **W1** but then combined it with the bigger fragment **W2** without the ketone to give **W3**. In doing this they showed that the ketone in **25** is actually more electrophilic than the epoxide. It is not always possible to be certain which of two functional groups is the more reactive but this can be determined experimentally and the strategy altered accordingly.



Compound Numbers in the Workbook

Since much of the workbook refers directly to the main text *Organic Synthesis: Strategy and Control*, all plain compound numbers in the workbook refer to the same compound in the same chapter of the main book. Compounds in the workbook but not in the main text are given numbers with a **W** prefix. So compound **34** is the same as in the main text but compound **W34** is a workbook compound. Workbook numbers start afresh with **W1** in each chapter.

References

1. K. C. Nicolaou and P. S. Baran, *Angew. Chem., Int. Ed.*, 2002, **41**, 2678.
2. H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2005.

3. M. A. Sierra and M. C. de la Toore, *Angew. Chem., Int. Ed.*, 2000, **39**, 1539.
4. J. Cossy, F. Pradaux and S. BouzBouz, *Org. Lett.*, 2001, **3**, 2233; Y. K. Reddy and J. R. Falck, *Org. Lett.*, 2002, **4**, 969; Y. G. Wang and Y. Kobayashi, *Org. Lett.*, 2002, **4**, 4615; T. Esumi, N. Okamoto and S. Hatakeyama, *Chem. Commun.*, 2002, 3042; K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi, S. Tamura and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 17111.
5. D. E. Chavez and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2001, **40**, 3667.