The Role of Symmetry in Synthetic Analysis. The Concept of Reflexivity

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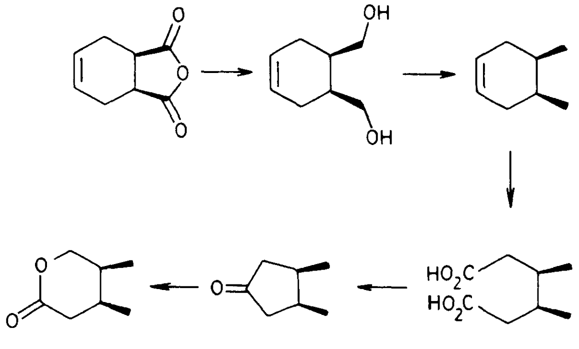
Molecular symmetry can complicate or simplify a synthetic problem (conditions are given for each case); however, symmetry in a synthesis graph (synthetic plan) is always a simplifying factor.

Symmetry is arguably the most important concept in science,[1] and it has a major role in our understanding of chemistry.[2] Most applications to date have been in quantum chemistry, where the presence of symmetry can greatly simplify the calculation of molecular energy levels.[3] It has also been stated that symmetry is a simplifying factor in the synthesis of complex molecules;[4—6] however, the situation here is more subtle than previously realized, especially as it relates to the principle of convergence.[7—9]

It has been suggested that the identification of symmetrical starting materials is an important goal of retrosynthetic analysis;[6] however, careful scrutiny of the examples cited suggests that in these cases, and in many like them, symmetrical starting materials (or intermediates) should be avoided. For example, in the Gates synthesis of morphine from 2,6-dihydroxynaphthalene,[6,10] the first step involves the differentiation of the hydroxy groups, for which 'a procedure which produces the monobenzoate in yields as high as 71% was developed.'[10] The yield of monobenzoate was limited by the 25% of dibenzoate formed as the inevitable side-product. The most efficient approach[11] to morphine and its congeners proceeds from *m*-methoxyphenethylamine and 3-hydroxy-4-methoxyphenylacetic acid, which are not symmetrical. Thus, symmetry is undesirable if it must be broken on the way to the target, and if a *control strategy* cannot be found to improve on the statistical result.

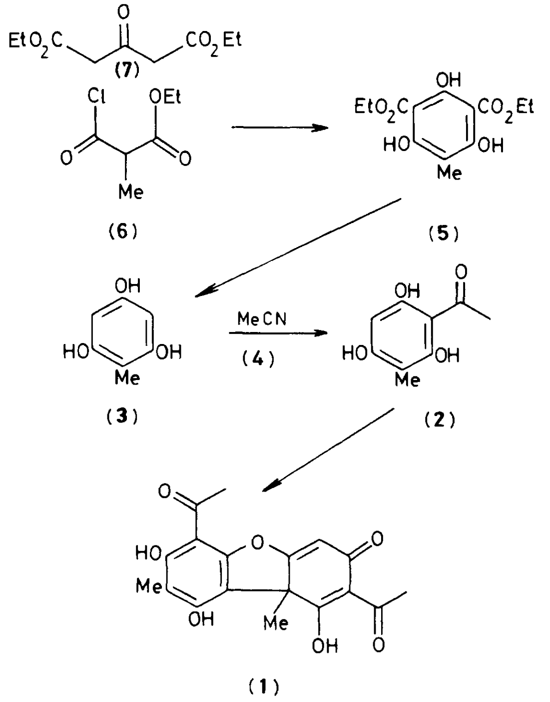
Proximity is the most general control strategy: reaction at one of the symmetrical sites must alter the steric or electronic nature of the other site(s) so that the same process will not be repeated there. Simple examples are the reaction of succinic anhydride with alkoxide to obtain the half-ester,† and the Baeyer–Villiger oxidation of cyclopentanone to δ-valerolactone.[12] As these examples also illustrate, *symmetry is beneficial when it obviates the need for selectivity*, in these cases between the carbonyl groups of succinic anhydride and the methylene groups of cyclopentanone, respectively. In contrast, the reaction of alkoxide with α-methylsuccinic anhydride[13] and the Baeyer–Villiger oxidation of 3-methylcyclopentanone are not chemoselective. In the enzymatic production of (3*S*)-3-methyl-δ-valerolactone, the use of a symmetrical substrate, 3-methylpentane-1,5-diol, 'has the great advantage that it avoids the inevitably lower (50% maximum) yields of a desired stereoisomer obtained when the substrate is a racemate [the corresponding hemiacetal].'[14] In the case of 3,4-dimethylcyclopentanone, the selectivity problem is again obviated by symmetry in a key step of Baker's faranal synthesis (Scheme 1,‡ last step).[15] Another example from this synthesis is the Dieckmann cyclization (Scheme 1, fourth step), which does not require selectivity with regard to which carbonyl is attacked by which methylene.



Scheme 1

Symmetry can also be used to advantage if *an element of symmetry is maintained during the course of a synthetic sequence*, as in Scheme 1. Efficiency, measured in terms of overall yield or time saved (or both), is improved by enabling reactions to do double duty, thus reducing the number of steps. For a more sophisticated example, a C_2-axis is maintained in the intermediates during the early stages of Paquette's recently completed (linear) synthesis of dodecahedrane.[16] McKervey's and Ferguson's 'apple peel' approach to dodecahedrane from bicyclo[3.3.0]octane-2,6-dione makes even fuller use of this strategy.[17] A convergent synthesis of dodecahedrane based upon the dimerization of triquinacene has yet to be achieved, owing in part to the large excess complexity[9] that results from the different functionality introduced into the two halves in order to obtain selective *endo–endo* dimerization.[18]

Symmetry in a target molecule is not necessary in order to use symmetry in synthetic planning. *Symmetry in a synthetic*



Scheme 2

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†This example is taken from ref. 23, p. 39.

‡ Only one enantiomer is drawn.

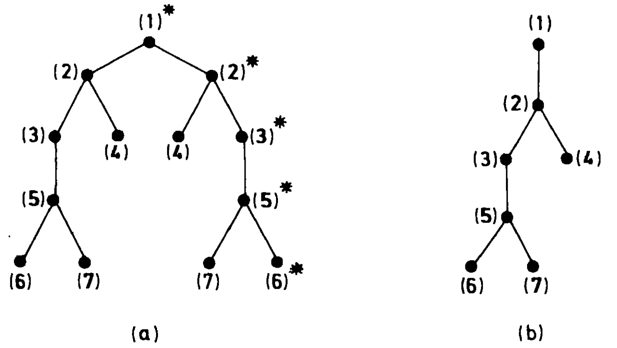

Figure 1. Synthesis graphs for (a) labelled and (b) unlabelled usnic acid following Scheme 2.

plan is a powerful simplifying principle. As illustrated by the classic Barton synthesis of usnic acid (**1**)[19] (see Scheme 2), the advantages of this approach lie not only in the usual economies of a convergent synthesis,[7–9] but also in the fact that the two pieces joined in the convergent step are *identical*. Consequently, both branches of the synthesis graph[8] (synthetic tree[4]) are identical, and collapse into a single path. (This is most easily visualized by comparing synthetic trees for labelled and unlabelled usnic acid, see Figure 1.) Such a synthetic plan may be called *reflexive*,§ and is much more efficient (approx. half the work involved) than an ordinary convergent synthesis in which the two branches are different. Potential symmetry' has been used to describe this concept;[4] however, as shown here, real symmetry is present—in the synthesis graph. Neither (**1**) nor (**2**) is a symmetrical molecule; it is the symmetry in the synthesis graph which is responsible for the elegance of this approach. Other examples of molecules that can be approached in this way are the bis-alkaloids, *e.g.* emetine.[20] If the target molecule does have a non-trivial element of symmetry, then the reflexive, convergent approach is readily identified, as in Stork's synthesis of α-onocerin[5,21] and Seebach's syntheses of pyrenophorin and vermiculin,[22] which have C_2 symmetry.

Of course reflexivity does not guarantee success any more than convergence does. As Warren points out in his caveat about convergent syntheses, 'one bad step can be just as disastrous here as elsewhere.'[23] For example, the direct dimerization of triquinacene to dodecahedrane has yet to be reduced to practice.[18] This would epitomize a reflexive, convergent synthesis, whereas the preparation of dodecahedrane from differently functionalized triquinacenes[18] would be convergent, but not reflexive, and not especially efficient (*vide supra*). Therefore, the convergent approach should be modified to use the same functionality on both triquinacenes, thereby making it reflexive.

It can now be appreciated how reflexivity differentiates the two alternative conceptual approaches to enantioconvergent synthesis.[24] The conversion of enantiomers to the same target by different routes is convergent but not reflexive, as the synthesis graph has two distinct branches. An example of this approach is the prostaglandin synthesis of Newton and Roberts,[25] in which an enzymatic reduction of an unsymmetrical (±)-ketone (bicyclo[3.2.0]hept-2-en-7-one)¶ yields two diastereoisomeric alcohols, which are carried on to the target *via* two independent routes. In contrast, only one route had to be developed in Trost's reflexive synthesis of prostanoids,[24] which uses an intermediate that allows the ready interconversion of enantiomers by a simple chemical reaction (in conjunction with a method for biasing the enantiomeric ratio, of course). Its reflexivity can be understood by noting that before the interconversion step as well as after it, all molecules are carried through the synthetic sequence together, along the same path of the synthesis graph.

It may be hoped that this communication has led to a deeper understanding of the role of symmetry in synthetic planning. The synthesis graph should no longer be considered a mere pictorial representation of a synthesis plan, as its symmetry properties** are useful in synthetic planning.

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§ $A = A$ is the reflexive property of algebra.

¶ Had the ketone been a symmetric one, only one product would have been obtained, see ref. 14.

** For an algorithm that determines the symmetry properties of a graph, see W. C. Herndon and J. E. Leonard, *Inorg. Chem.*, 1983, **22**, 554.