Learning Organic Chemistry Through Natural Products

6. Architectural Designs in Molecular Constructions

N R Krishnaswamy

We will discuss in this article an outline of the biosynthesis and a few laboratory-designed syntheses of camphor.

In the first two articles of this series we saw how the structures and conformations of naturally occurring compounds could be determined. In the third and fourth we discussed the relationships between structure on the one hand and chemical and biological properties on the other. The fifth was designed to give you some practical experience in isolation of a few of these compounds from their natural sources. In this sixth and final part of the series we shall illustrate with the help of an example how the construction of a molecule is designed and executed in nature and in the laboratory.

Total laboratory synthesis and biosynthesis of natural products are complementary in the sense that if one is the end product of human intellect, ingenuity and technical and experimental skills, the other is the result of what one may sum up as the total wisdom of nature evolved over millions of years. We do not know how this wisdom was evolved and what the motivating forces were. We also do not know whether the chemistry of the secondary metabolites present in plants, insects, animals etc of the present time is the same as that of the earlier generations and whether it would remain the same in the future. We can only guess that the answer is 'perhaps not', if the understanding of the role of metabolites is correct. With the changes in the environment, however subtle and slow, there have to be corresponding changes

N R Krishnaswamy was initiated into the world of natural products by T R Seshadri at University of Delhi and has carried on the glorious tradition of his mentor. He has taught at Bangalore University, Calicut University and Sri Sathya Sai Institute of Higher Learning. Generations of students would vouch for the fact that he has the uncanny ability to present the chemistry of natural products logically and with feeling.

Box 1

For a small molecule, camphor, perhaps, is one of the most agile and articulate compounds known. It has a characteristic smell and is widely used as deodorant and insect repellent. Camphor is optically active and both the (+) and (-) forms as well as the racemate occur in nature. (+) Camphor is obtained from the wood of the camphor tree, *Cinnamum camphora* where-as the (-) form is isolated from the essential oil of *Matricaria parthenium*. Racemic camphor occurs in *Chrysanthemum sinensis*.

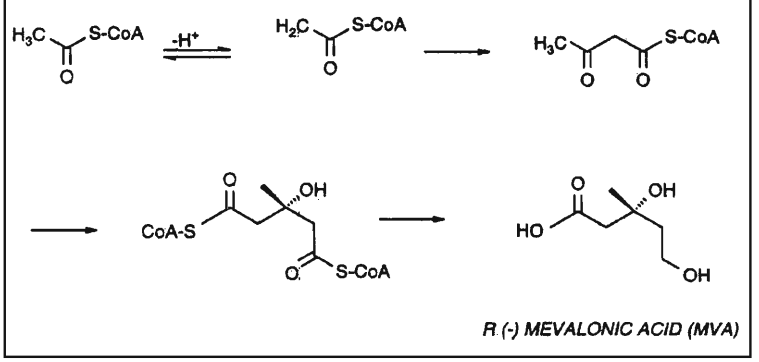
in the strategies used for self-defence and survival of the species. We do hope that some of our young readers would think of this and devise appropriate methods of investigation which could give answers to these questions. As was pointed out earlier (in different terms) present day chemistry of natural products is equivalent to lifting the curtains that block our view of the drama being continuously enacted in nature; only a part of the action has been unveiled. We see only what has been created and is existing. What is more interesting is to know who or what (if an answer to this question could ever be found!), why and how the script was prepared for this grand show. That is, indeed, a tall order and a challenge for the bravest and most daring!

We will discuss in this article an outline of the biosynthesis (omitting biochemical details) and a few laboratory-designed syntheses of camphor. This important and well known naturally occurring ketone (*Box 1*) is a monoterpene and is biosynthetically derived from R (–) mevalonic acid. Mevalonic acid itself is synthesised from three acetic acid units. Each acetic acid is first 'activated' by conversion into acetyl coenzyme-A. In this step we see that nature is aware of the need to replace hydroxyl of the carboxylic acid with a better leaving group before the carbonyl of the carboxyl function can easily be attacked by a nucleophile. In the laboratory a carboxyl group is usually activated by conversion into its anhydride or acid chloride (*Box 2*). Nature uses coenzyme-A which has a sulfhydryl (SH) group which undergoes acetylation. Acetyl coenzyme-A can also lose a proton to generate a carbanion which then attacks the carbonyl group of another

Box 2

The acid chloride and the anhydride are more reactive than the free acid because the chloride and carboxylate ions are better leaving groups than OH Activation of the carboxyl group is an essential prerequisite in peptide synthesis.

Scheme-1



R (-) MEVALONIC ACID (MVA)

acetyl coenzyme-A molecule as shown in *Scheme-1*. The product is a thioester which also has a keto carbonyl group. Reaction of this compound with the carbanion of a third acetyl coenzyme molecule at the keto carbonyl group results in a compound having six carbon atoms. This reaction is a biochemical equivalent of aldol condensation (*Box 3*). Reduction by hydride ion transfer (*Box 4*) of one of the thioester groups to the corresponding alcohol and hydrolysis of the other leads to mevalonic acid as shown in the Scheme. The compound has an asymmetric carbon and therefore, two enantiomorphic forms are possible. Natural mevalonic acid has the R configuration and is laevo-rotatory (*Box 5*)

Scheme-2 shows the biochemical conversion of mevalonic acid into isopentenyl pyrophosphate and then on to geranyl pyrophosphate. This transformation takes place in several steps. In the first step, the primary hydroxyl of mevalonic acid is converted into its pyrophosphate. This reaction is brought about by an enzyme which requires adenosine triphosphate (ATP). Mevalonic acid pyrophosphate then undergoes dehydrative decarboxylation in the presence of ATP to yield isopentenyl pyrophosphate (IPP). Isomerization of IPP results in dimethylallyl pyrophosphate (DMAPP). Combination of one IPP molecule with one DMAPP then gives geranyl pyrophosphate.

Box 3

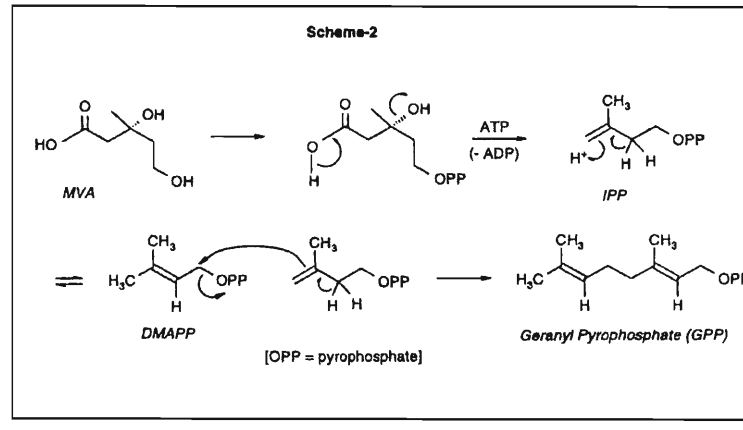
The aldol condensation is one of the widely used reactions in preparative organic chemistry. The classical example of this reaction, which can be catalysed either by a base or by an acid, is the self condensation of two molecules of acetaldehyde. A crossed aldol reaction involving two different aldehydes or ketones is also known as the Claisen-Schmidt reaction.

Box 4

Reductions by hydride ion transfer occur in nature through the mediation of the coenzyme NADH (the reduced form of nicotinamide adenine dinucleotide). In the laboratory, a similar function is performed by metal hydrides such as sodium borohydride and lithium aluminium hydride as well as aluminium isopropoxide (Meerwein-Pondorff-Verley reduction).

Box 5

In contrast to most laboratory reactions, biochemical reactions result in the formation of one of the enantiomorphs of an optically active compound. This is a consequence of the fact that these reactions are catalysed by enzymes which themselves are chiral in character.

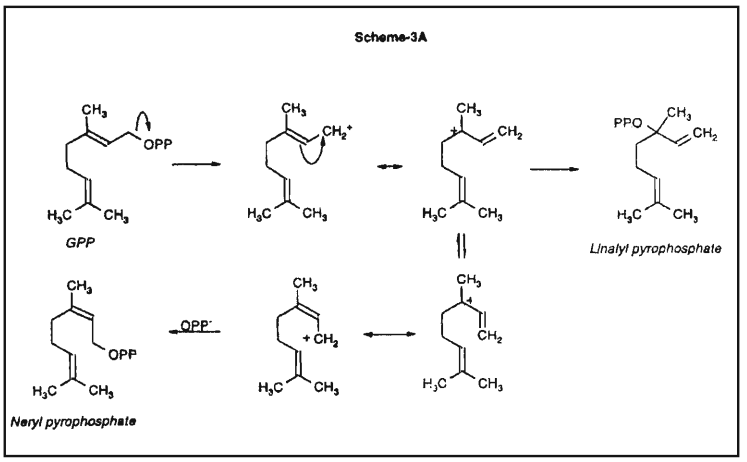


Geranyl pyrophosphate can isomerise into neryl pyrophosphate and linalyl pyrophosphate (*Scheme-3A*). Such an isomerism occurs with ease since the pyrophosphate group is a good leaving group and is also a nucleophile. Linalyl pyrophosphate loses the phosphate grouping with the simultaneous interaction of the two double bonds as shown in *Scheme-3B*. The result is a carbocation with a six membered ring. It is important to note that such a cyclisation requires the appropriate conformation of the acyclic precursor as indicated in the Scheme. This carbocation can stabilise itself in several possible ways, one of which is an intra molecular interaction between the cationic center and the endocyclic double bond.This reaction itself can occur in either of two ways, one leading to the pinene structure and the other to borneol as shown in the Scheme. Oxidation of borneol gives camphor. This series of reactions can be used to illustrate the nuances in nucleophilic substitution reactions and the generation and fate of carbocations. Figure out for yourself the other possible modes of stabilisation of the afore mentioned carbocation (*Box 6*).

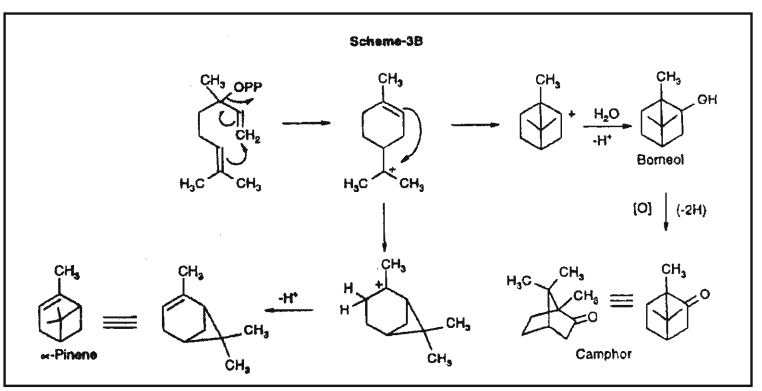
Box 6

The bicyclic monoterpenoids produced from this carbocation include, besides compounds having pinane and bornane structures, those derived from carane and thujane, each of which has a cyclopropane ring.

Komppa's synthesis of camphor was a classical example of a total synthesis designed for confirming a structure deduced from analytical and degradation studies. A key intermediate was camphoric acid which was synthesised starting from diethyl oxalate. The sequence involved several well known and



unambiguous reactions such as Claisen condensation, base catalysed C-methylation and Meerwein-Pondorff-Verley reduction. We will not discuss this synthesis here, since a description of this can be found in several text books of organic chemistry. We will, instead, describe three newer and shorter methods of synthesis. In one of them the primary target molecule is camphene which is then converted to camphor via isoborneol (*Scheme-4*). The first step is a Diels-Alder reaction (*Box 7*) between cyclopentadiene and mesityl oxide. Subsequent steps involve catalytic hydrogenation, a haloform reaction, reduction of carbonyl to CH_2OH group and dehydration via the tosyl ester. Camphene (*Box 8*) thus obtained is converted into camphor in two steps.



Box 7

The Diels-Alder reaction is one of the most popular among preparative organic reactions as it is stereospecific. It is a thermally allowed cycloaddition reaction between a diene and a dienophile and comes under the broad class of pericyclic reactions. The Nobel laureates Woodward, Hoffmann and Fukui, put forward a theoretical framework for understanding the mechanism of this and other pericyclic reactions.

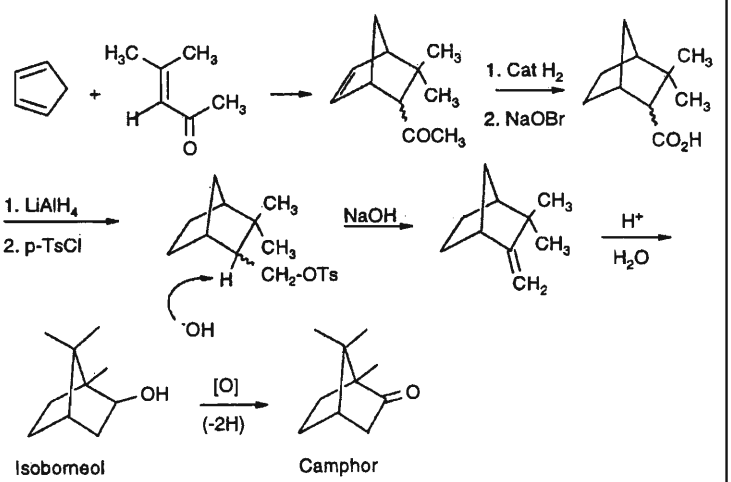
Box 8

(-) Camphene is a crystalline bicyclic monoterpene hydrocarbon which was first isolated in 1888 from the essential oil of *Abies sibirica*. It can also be obtained from alpha-pinene and can be converted in turn, into camphor via isobornyl acetate. In these transformations, Wagner-Meerwein rearrangements play a major role.

Box 9

A regiospecific reaction is one in which one single structural isomer is formed exclusively. The reaction under discussion is not regiospecific as both the possible structural isomers are obtained. From the preparative point of view, a regiospecific reaction is to be preferred to a non-regiospecific reaction.

Scheme-4

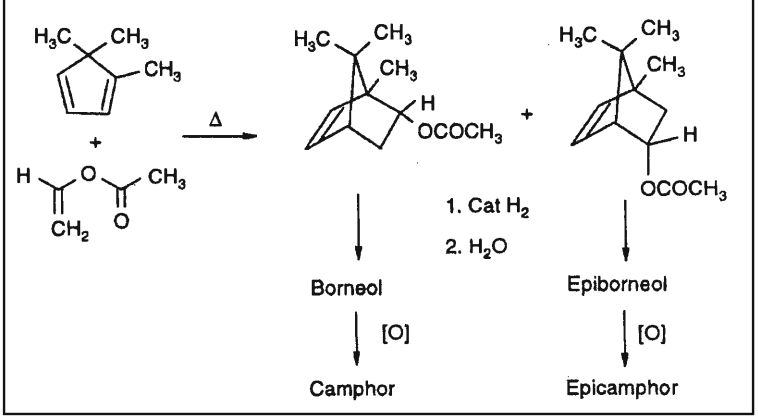


A Diels-Alder reaction is the first step in another direct synthesis of borneol wherein the starting materials are 1,5,5-trimethylcyclopentadiene and vinyl acetate. However, this reaction is not regiospecific (*Box 9*) and a mixture of bornyl and epibornyl acetates is obtained. Hydrolysis and oxidation yield camphor and epicamphor as shown in *Scheme-5*.

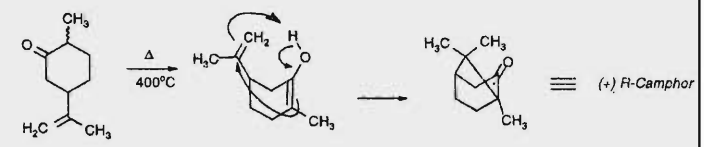
Box 10

An asymmetric synthesis is one wherein one enantiomorph of a chiral compound is formed either exclusively or as the major product. The reaction described here is a good example of an asymmetric synthesis as the product is 80% optically pure.

Scheme-5



Scheme-6



The third synthesis is an asymmetric synthesis (*Box 10*) in which (+) camphor of 80% optical purity is produced by heating (+)-dihydrocarvone at 400°C. The enol form of the ketone undergoes an ene reaction as shown in *Scheme-6*. Try to understand the mechanism of each step of the above synthetic sequences as it is the key to the understanding of organic reactions. Camphor is not a particularly complex molecule but the syntheses described herein do have ingenuity and an elegant architectural planning.

Address for Correspondence
N R Krishnaswamy
No.12, 9th Main Road
Banashankari 2nd Stage
Bangalore 560 070, India

It is necessary to emphasise that in these six articles we have only touched the fringes of the chemistry of natural products. But in doing so, we hope we have been able to give you a fairly clear overall picture. Conventionally, natural product chemistry is taught as a (large) chapter within organic chemistry. The reality, however, is that it is organic chemistry (with an addendum trailing into biology) magnified several times. All aspects of organic chemistry with all their nuances can be taught and learnt using natural products as illustrative examples. This has been the main objective of this series of articles. Learning (any subject) is largely a personal experience and the major function of a good book is to provide the right kind of framework, incorporating factual material with a sense of priority as to what is more important and what is less. A book has its own limitations, the major restricting factor being space. This constraint is more pronounced in an article appearing in a journal. A good teacher fortifies what she/he gets from a reliable book with additional material gathered from other sources, edits them to weed out trivialities, and translates this impersonal, very often 'dry' (but accurate) parcel of information into something lively, attractive and palatable. Her (his) main function is to instill a craving for knowledge and stimulate thinking and reasoning power in her (his) students. If a good book is comparable to a Shakespearean play (for example, Hamlet), a teacher's performance in the class room must resemble interpretation by someone like Sir Laurence Olivier! Those of us who have had the good fortune to learn the chemistry of natural products under outstanding masters know that the subject is no less enjoyable than a Shakespearean drama. We do not know how far we have succeeded in conveying to our readers the beauty and richness of the subject through these six articles. We would like to hear from students who have read these articles.