

# Learning Organic Chemistry Through Natural Products

## 1. Natural Products - A Kaleidoscopic View

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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 traditions 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.

**A naturally occurring organic compound has been chosen to illustrate (a) structure determination by chemical and spectroscopic methods, and (b) synthesis and chemical transformations.**

Organic chemists isolate or synthesize new compounds all the time. How does one identify their structures? Some may answer — “X-ray”! However, X-ray diffraction can be used to determine structures only for compounds which form single crystals. For the vast majority of organic compounds, structure elucidation is carried out by a combination of chemical transformations and spectroscopic analyses. In this article we discuss the general approach that is followed using a natural product as an example.

In order to keep the focus on chemistry, we defer giving its trivial name and plant source till the end of the discussion. An additional bonus of such an approach is that the student logically deduces the structure from the given set of data and does not merely recall the structure from memory. Further, wherever possible we look at a problem from different angles thus covering a wider ground.

As our first example we choose a molecule, designated as **A**. We describe two different analytical approaches and a synthetic approach for elucidating and confirming its structure. The classical method which has developed over the years from a large volume of experimental work will be described first.

The first step in structure elucidation is the determination of the correct molecular formula, which for compound **A** is  $C_{10}H_{18}O$ .<sup>1</sup>

<sup>1</sup> Empirical formula is determined from combustion analysis.

<sup>2</sup> Thin layer chromatography (TLC) is an analytical tool to separate compounds based on their differential interactions with a stationary phase and a moving solvent. A species with a greater relative affinity for the solvent moves faster (higher  $R_f$  value) on a TLC plate.



### The Series on "Learning Organic Chemistry Through Natural Products"

Nature is a remarkable and excellent teacher. For effective learning, one needs a suitable language and the language of organic chemistry appears ideal for understanding nature at the molecular level.

The molecules of nature, the small and the big, individually and collectively give form, shape and substance to the living organisms in which they occur. The key to their biological functions is their chemistry which in turn is intimately associated with their structures. Therefore, the first step in the study of biomolecules is to find out their structures and stereochemistry. Next, the reaction profiles of a molecule need to be established as they enable us to understand the biological activity. An organic chemist does not just stop at that, but goes further by creating it ingeniously in the laboratory using tools of her own. This *synthesis* is an integral part of organic chemical research and the inspiration for it is provided by nature. Thus, the chemistry of natural products forms a wide canvas portraying every kind of organic chemical activity and going beyond. It acts

\*A structure is like a skeleton. What gives it 'life', like flesh and blood, are the bonding and the non-bonding electrons incorporated in the structure.

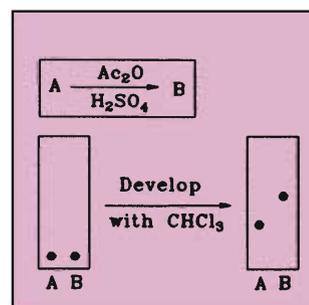
as a bridge for transferring principles and concepts of chemistry to the biosciences thus providing a molecular basis for biological phenomena.

How does effectively learn a subject of such vast dimensions within a short time is an intriguing question. At present organic chemistry is taught in a narrative form and the student is compelled to memorise a vast amount of descriptive data and a wide variety of apparently unconnected structures. It is therefore not surprising that the subject is not favoured by serious students seeking intellectual contents. This is unfortunate since half a dozen carefully chosen natural products can take a student to every nook and corner of organic chemistry, and illustrate and highlight important guiding principles of the subject. This can be done by removing artificial barriers which at present divide natural products into various structural categories. \*Therefore, when one shifts the focus from the gross skeletal structure to the interior electronic configuration, the need for classification based on structural types loses importance, and the emphasis shifts to fundamental chemical principles which are few and unifying.

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What is the next step? The functional groups are to be determined now. The nature of the oxygen functionality is shown by a simple reaction which can even be demonstrated on a thin layer chromatogram.<sup>2</sup> The adjacent picture shows the TLC behaviour of **A**, and the product obtained after treatment with acetic anhydride or sulphuric acid.

From the chromatogram it can be inferred that **A** has a hydroxyl



group since it undergoes acetylation. **B** moves higher with the solvent (higher  $R_f$  value) indicating its weaker interaction with the silica surface.

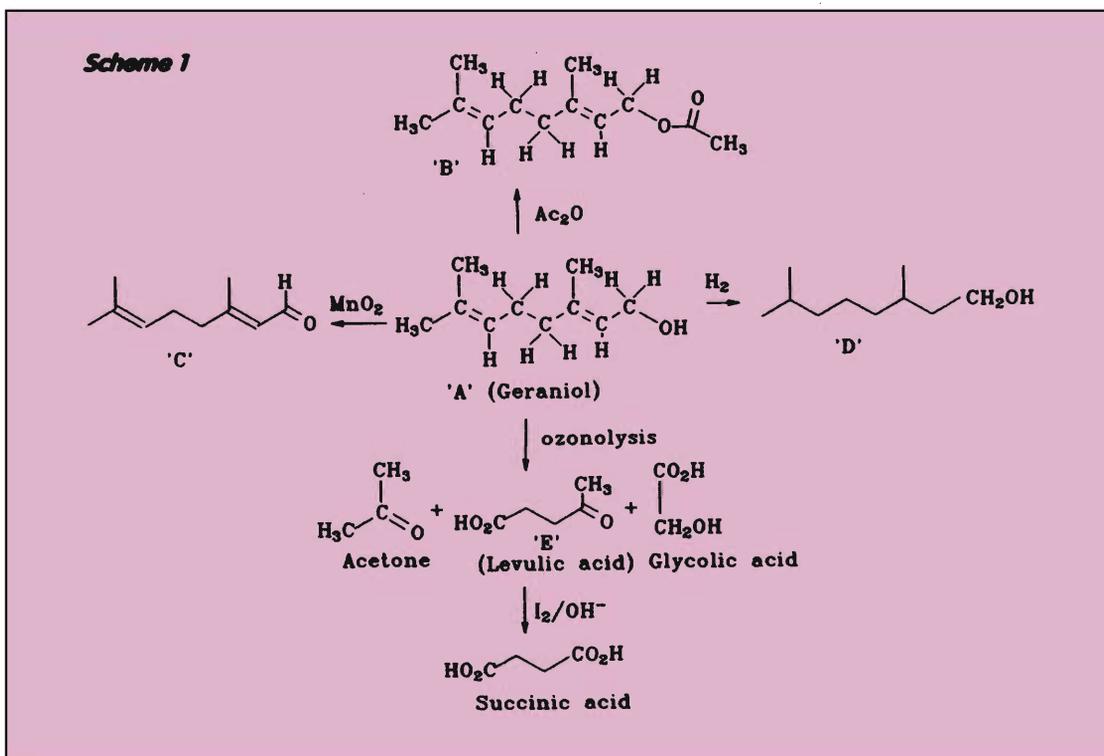
<sup>3</sup> (a)  $MnO_2$  is a specific oxidant for allylic and benzylic alcohols, (b) DNP derivatives of saturated carbonyl compounds are *pale yellow*, whereas highly conjugated compounds like benzophenone give *brick-red* products with DNP.

**A** can be oxidised with  $MnO_2$  to yield **C** ( $C_{10}H_{16}O$ ) which forms an *orange-red* derivative with 2,4-dinitrophenylhydrazine (DNP).<sup>3</sup> These observations suggest that **C** is an  $\alpha, \beta$ -unsaturated aldehyde or ketone. Compound **C** does not answer the iodoform test ( $I_2/OH^-$ ), but reduces Tollen's reagent, suggesting that it is not a methyl ketone, but an aldehyde.

<sup>4</sup> Ozonolysis cleaves a double bond to produce two carbonyl compounds. Oxidative workup converts an aldehyde to the carboxylic acid. Ketones are unaffected.

**A** on catalytic hydrogenation gives a *tetrahydro* derivative **D** ( $C_{10}H_{22}O$ ), showing thereby that it has two double bonds. The molecular formula of **D** also shows that it is a saturated alcohol. *Therefore, A is a doubly unsaturated, acyclic allylic primary alcohol.*

Ozonolysis of **A** followed by oxidative workup<sup>4</sup> yields one molecule each of acetone, glycolic acid, and a keto carboxylic acid **E**



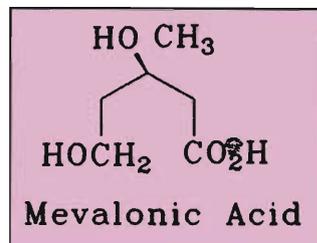
( $C_5H_8O_2$ ). Compound **E** on treatment with  $I_2/OH^-$  gives succinic acid. These reactions are shown in *Scheme 1*. The keto acid **E** could therefore be identified as levulinic acid. The structure of **A** can thus be logically derived as shown in the scheme. This compound is *Geraniol* which is a component of several essential oils including the oil of Geranium.<sup>5</sup>

We will now describe an alternative approach based on modern instrumental methods for finding out the structure of geraniol.<sup>6</sup> Among the advantages of this approach are the fact that unlike the classical chemical method, it is by and large non-destructive and can be operated on micro quantities of the compound. But the data obtained from the two approaches are not the same and, taken together, they give a more complete picture of the molecule than that available from either set of data. Therefore the best approach to structure determination would be a judicious combination of spectroscopic methods with a few selected chemical transformations.

In order to determine the *chromophoric* ('colour producing') groups a UV/Vis spectrum can be taken.<sup>7</sup> The UV spectrum of a methanolic solution of **A** shows an intense absorption at about 205 nm. In the UV spectrum of **C**, there are two absorption maxima at 205 and 232 nm. The inferences are: **A** has two similar, if not identical chromophores. The position of the absorption maxima indicates that they are trisubstituted ethylenic double bonds. In **C**, one of these chromophores is retained while the other, responsible for the maximum at 232 nm, is an  $\alpha, \beta$ -unsaturated aldehyde.

The IR spectra of **A** and **C** provide important information.<sup>8</sup> The spectrum of **A** has a broad band at  $3350\text{ cm}^{-1}$  which is absent in the spectrum of **C**. This band is due to a hydroxyl group. The spectra of both **A** and **C** have bands at  $3040$  ( $=C-H$ ),  $2920$ ,  $2860$  and  $1350$  ( $CH_2$  and  $CH_3$  groups)  $\text{cm}^{-1}$ . These bands show that **A** and **C** possess an aliphatic skeletal framework with one or more double bonds. The most prominent absorption band in the spectrum of **C** is seen at  $1680\text{ cm}^{-1}$  which is absent in the spectrum of **A**. This

<sup>5</sup> Biosynthetically, geraniol is the first member of the terpenoid family arising from two units of mevalonic acid.



<sup>6</sup> The following five paragraphs contain advanced material, and will require some knowledge of spectroscopy.

<sup>7</sup> UltraViolet absorption arises due to *electronic excitation* of functional groups called *chromophores*. For example, in an olefin it is an electronic transition from the  $\pi$ -orbital to the  $\pi^*$ -orbital.

<sup>8</sup> InfraRed spectroscopy is used to characterize vibrational (stretching, bending etc) energy levels of molecules. Groups such as O-H, C-H, C=O can be easily identified from IR spectra. The nature of the C=O (e.g., acid chloride, amide, ester etc.) can also be determined.

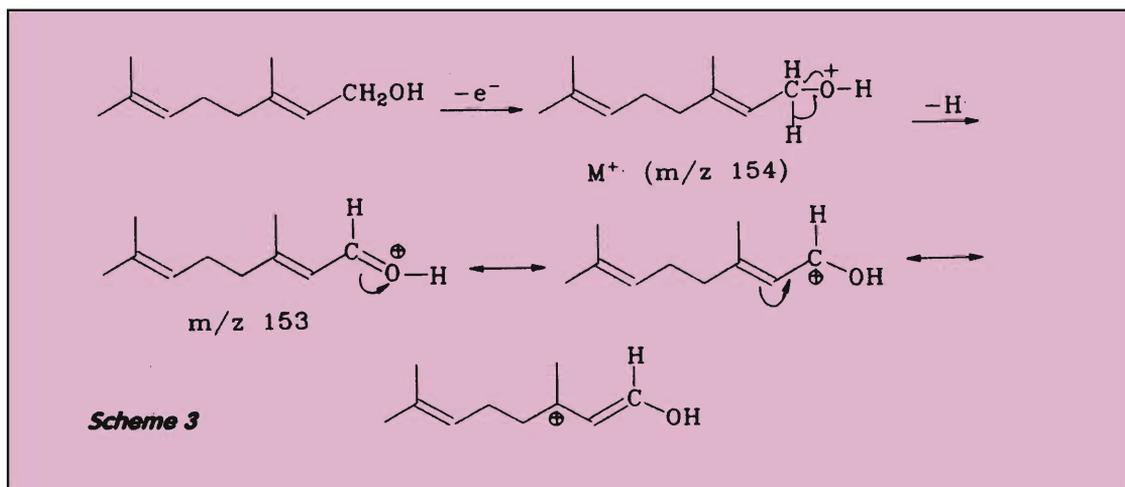
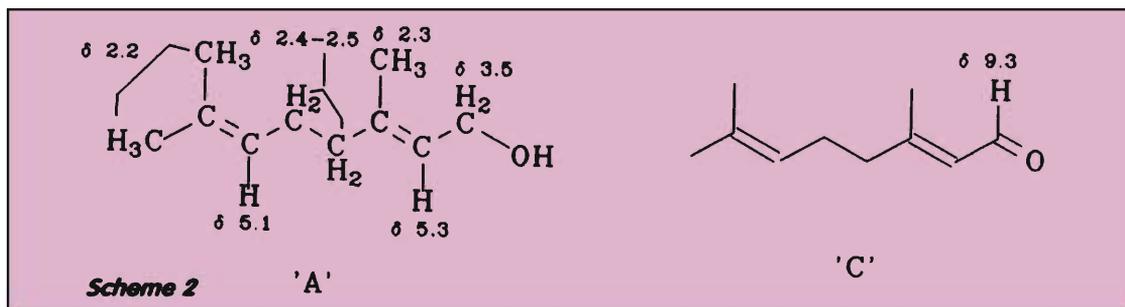


<sup>9</sup> Nuclear magnetic resonance is a technique in which the energy levels of magnetic nuclei can be observed by looking at the absorption (resonance) of electromagnetic radiation in the presence of an external magnetic field. Hydrogen is one such nucleus, and the chemical environment of the hydrogen affects the resonance frequency making it a valuable analytical tool for chemists. This resonance frequency, converted to a parts per million dimensionless scale, is reported as the  $\delta$  value. Typically, higher the partial positive charge on a hydrogen atom, higher is its  $\delta$  value.

band is due to the  $\alpha, \beta$ -unsaturated carbonyl group. The presence of the CHO group in C is also indicated by a band at  $2800 \text{ cm}^{-1}$ .

The <sup>1</sup>H-NMR spectra of A and C provide the most compelling evidence for their structures.<sup>9</sup> The spectrum of A has signals at  $\delta 2.2$  (s, 6H), 2.3 (s, 3H), 2.4–2.5 (m, 4H), 3.5 (d, 2H), 5.1 (t, 1H) and 5.3 (t, 1H). These data show the presence of three methyl groups on  $\text{sp}^2$  carbons, two olefinic hydrogens (each on a carbon atom next to a  $\text{CH}_2$  group as the signals appear as triplets), and a  $\text{CH}_2\text{-CH}_2$  unit. The signal at  $\delta 3.5$  is due to the  $\text{-CH}_2\text{OH}$  end group next to an  $\text{sp}^2$  carbon. This signal shifts to  $\delta 4.5$  upon acetylation of A. From these data it is possible to deduce the structure of A as shown in Scheme 2.

In the NMR spectrum of C, the two proton signal at  $\delta 3.5$  is missing, and instead, there is a one proton doublet at  $\delta 9.3$ , due to the aldehydic proton.



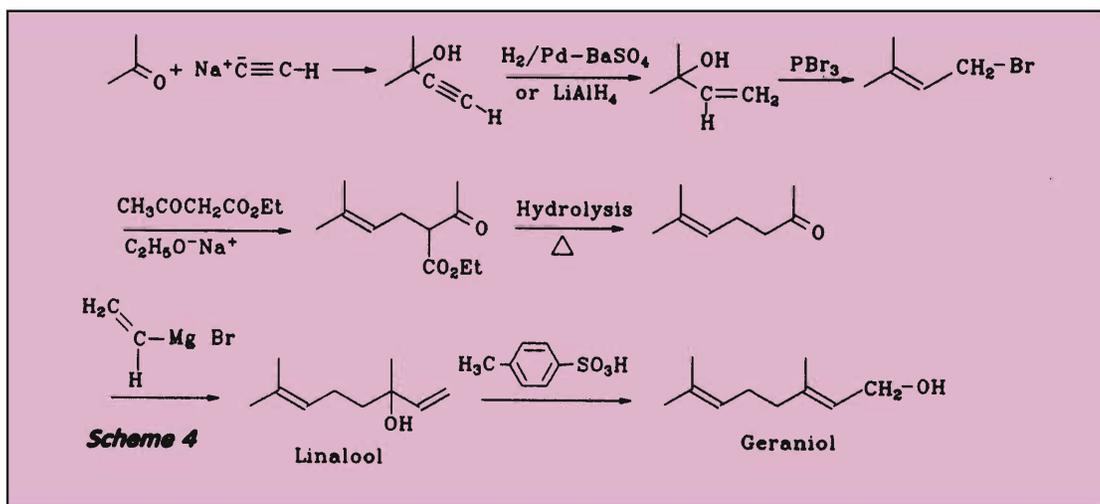
*Scheme 3* gives the mass spectral fragmentation of A.<sup>10</sup> Besides the molecular ion signal at  $m/z$  154, there is a prominent peak at  $m/z$  153. This can be accounted for in mechanistic terms, and lends strong support to the structure.

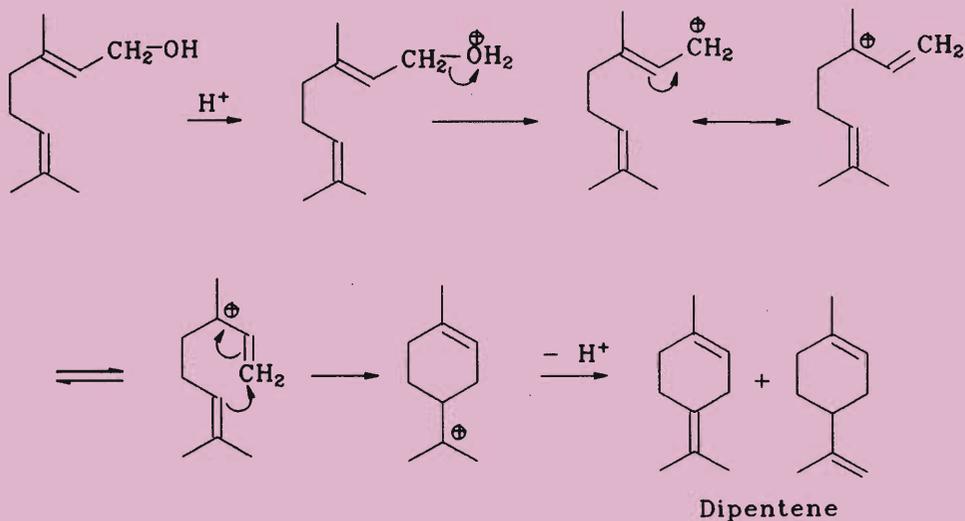
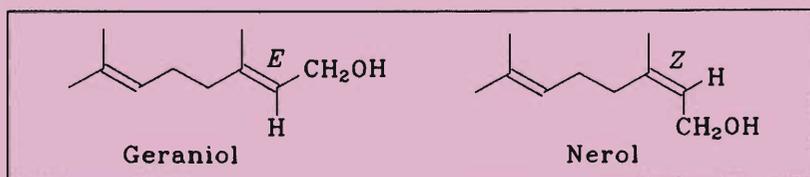
Finally, the structure of geraniol is confirmed by synthesis. Whereas the analytical approach involves the dissection of the molecule into smaller recognizable units, the synthetic approach involves the reconstruction of the proposed structure from smaller molecules using predictable and unambiguous reaction pathways. One synthetic approach is shown in *Scheme 4*. Explanatory notes have been deliberately omitted as the students should themselves logically determined each and every step of the reaction sequences.

We conclude this brief account of the chemistry of geraniol with a short note on its stereochemistry. This compound is optically inactive and non-resolvable, but can assume several conformations. On acid catalyzed dehydration, geraniol yields dipentene as one of the products. The formation of this cyclic terpene which can be rationalized, as shown in *Scheme 5*, illustrates the importance of appropriate conformations in intramolecular reactions. This example can also be used for demonstrating the formation, stability and fate of a carbocation.

<sup>10</sup> Mass spectrometry, in its simplest form, involves ionization of a molecule with high energy electrons, and detecting ions, or their fragmented units according to their mass to charge ratio. This is a valuable tool for determination of the molecular mass, as well as for structure elucidation — since the fragmentation pattern is unique for a given molecule.

**The analytical approach involves the dissection of the molecule into smaller recognizable units; in the synthetic approach we reconstruct the proposed structure from smaller molecules using predictable and unambiguous reaction pathways.**




**Scheme 5**


As can be seen from the structure (box in Scheme 5), geraniol has the *E* configuration at the unsymmetrically substituted double bond. The *Z* isomer also occurs in nature and is known as nerol. Nature converts geraniol into nerol via geranyl pyrophosphate. The two configurational isomers (diastereomers) have separate existence. However, upon oxidation, both geraniol and nerol give a mixture of aldehydes (citral) which is an inseparable mixture of geraniol and nerol. (Can you explain why the two diastereomers of the aldehyde co-exist in contrast to those of the parent alcohol? A related problem is how you would prove that geraniol has the *E* configuration?)

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