Chapter 1: General Aspects

Part I: Synthesis in Perspective

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The term ‘synthesis’ is used in many contexts far removed from chemistry, e.g. philosophy and literature. In its broadest sense, synthesis means the tying together of individual pieces to construct or create a whole article. These activities of constructing or creating are inherent to mankind. In the context of chemistry, the definition of ‘synthesis’ is given in Kingzeit’s Chemical Encyclopaedia as ‘the building up of elements into compounds, or of compounds into more complex compounds’. ‘Synthesis’ in the chemical as well as in the more general sense is therefore a fascination and a challenge to the creative imagination.

It is not surprising that the brilliant colours of the carotenoids, designed by Nature to attract attention, should attract the attention of chemists to identify these molecules and then to recreate them by synthesis. Over the years, the challenge of synthesizing carotenoids has been taken up by many distinguished organic chemists, and procedures developed initially for carotenoid synthesis have found general application in organic chemistry. To the outsider, the non-chemist, such synthetic work looks very complex, and may seem to be just a difficult intellectual challenge. But synthesis is much more than this. The ability to synthesize a required structure at will is of immense benefit to other fields of science as well as providing the basis for major industrial activities. The fascination of carotenoids is still strong and indeed increasing as more and more biological functions and actions are revealed. Many problems still remain to challenge the ingenuity of the organic chemist and to allow synthesis to make increasing contributions to the exciting discoveries of other branches of science.

Looking back at the history of carotenoids, it is not surprising that the first target for synthesis was β,β-carotene (3), the substance that gave the name to the whole class of compounds and for which the correct structure was established in 1930. This labile molecule with its long conjugated polyene chain presented difficult practical problems that had not been encountered with other groups of natural products and required the development of new strategies and
methods, especially for constructing the polyene chain and linking together different parts of the molecule. The synthesis of β,β-carotene (3) was achieved independently by the schools of Karrer, Inhoffen, and Milas, in 1950, a year which can therefore be regarded as a milestone in carotenoid research. The principle of coupling appropriate end groups to a central building block that was established in this early work was developed further so that by 1976, 98 naturally occurring carotenoids had been synthesized. During this time many reactions, such as the Grignard reaction, enol ether condensations, aldol condensations and reactions via sulphones, were applied to construct the polyene chain. The synthesis of carotenoids was important in the development of organophosphorus chemistry through the Wittig and the Horner-Emmons reactions. Although the Wittig reaction, in which a carbonyl compound is reacted with a phosphonium salt, has certain disadvantages, such as the environmentally undesirable formation of triphenylphosphine oxide and sometimes the lack of selectivity and low yield, it is today by far the most important reaction for the synthesis of carotenoids because it allows the formation of carbon-carbon double bonds in a specific location in the molecule. The reaction was detected unexpectedly in 1953 and Wittig was awarded the Nobel Prize in 1979 for 'the development of phosphorus compounds into important reagents in organic chemistry'.

The pioneering synthetic work quickly led to the synthesis of carotenoids on an industrial scale. The industrial production of β,β-carotene (3) began in 1954, only four years after its first synthesis on a laboratory scale. This extremely rapid development was made possible by the enthusiasm and perseverance of Isler and his colleagues at Roche in Basel. Since then, commercial synthesis of carotenoids has continuously advanced and today the two major industrial producers Roche and BASF produce six different carotenoids, namely β,β-carotene (3), canthaxanthin (380), optically inactive astaxanthin (403) and the apocarotenoids 8'-apo-β-caroten-8'-al (482), 8'-apo-β-caroten-8'-oic acid (486) ethyl ester, and citranaxanthin (466). The total annual sale is now in the region of US$ 300 million, and the commercially produced carotenoids are used mainly as food and feed additives.

In 1957 a new era began with the synthesis of chiral carotenoids in optically active form, the first example being the naturally occurring (6'R)-β,E-carotene (7) and its enantiomer by the school of Karrer. The strategy used involved the resolution of the enantiomers of the end group synthon by separation of the diastereoisomeric menthyldrazones.

This classical approach of the resolution of a racemate into its enantiomers has the disadvantage that the maximum theoretical yield can never be greater than 50% if only one specific enantiomer is needed, and practical yields are normally much lower than this. On a preparative scale this is unsatisfactory or even unacceptable, especially if the separation is performed at a late stage of the synthetic pathway. It also requires reference data for compounds with known stereochemistry or alternatively X-ray structural analysis of the chiral synthon, in order to establish the configuration of the separated compounds.