Chapter 1: General Aspects

Part II: Strategies for Building the Carbon Skeleton

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A. Introduction

Modern synthetic organic chemistry would permit the preparation of carotenoids by an almost countless number of strategies. In reality, however, the few methods and strategies that became established early in this century have since been used repeatedly and some of these have been developed to the scale of industrial syntheses. The aim of this Chapter is to provide a guide to the simplest route to a particular target carotenoid.

B. General Strategies

The strategies for constructing a carotenoid can be divided into two main categories:

i) total or partial syntheses directed towards structure elucidation of isolated pigments,

ii) technical syntheses for production on an industrial scale.

In the early part of this century, the first procedures for the isolation of carotenoids and, subsequently, the first methods for systematic structure elucidation were developed. The initial synthetic procedures were limited to simple chemical modifications of the isolated carotenoids. These methods gradually lost their importance for preparative purpose because of the poor yields of such chemical transformations carried out on a chemically labile C_{40} polyene and the necessity to purify the products by extensive chromatography.

With the development of more sophisticated methods for carbon-carbon bond formation (see Chapter 2) came the era of directed synthesis. Among the first carotenoids to be formally synthesized was β,β-carotene (3) and the structurally related vitamin A (retinol).
In this Chapter, attention will be focused exclusively on total synthesis. In the ultimate step which leads to the target carotenoid there are theoretically two approaches, A and B, which could be used (Fig. 1).

![Diagram of theoretical approaches to the synthesis of a carotenoid](image)

**Method A:** double bond formation  
**Method B:** single bond formation

In method A, the building blocks are connected through the generation of a double bond by, for example, a Wittig reaction or a reductive elimination of a sulphone group (Julia olefination). Method B, in which a single bond between two double bonds is generated, was more or less neglected for a long time although modern synthetic methodology would enable the polyene chain to be formed with a defined (E/Z)-stereochemistry via e.g. Pd-catalysed coupling of suitable vinyl halides.

Based on the choice of method A or B for the final step and on the structure of the target carotenoid, the individual end groups and middle part can be defined (Fig. 2). There are either symmetrical (C₂-axes) or unsymmetrical carotenoids which are composed of the polyene chain, here called the middle part, and one or two identical or non-identical end groups, respectively. For connection of the middle part with the end groups by either method A or B in the case of a symmetrical carotenoid, the coupling may be accomplished in a single coupling reaction step. With unsymmetrical molecules, two different coupling reactions must be carried out separately. In this case, the middle part is joined to one end group and the intermediate thus formed is then coupled with a second end group.

The middle part is always a conjugated polyene (symmetrical or unsymmetrical) and can be prepared by a number of established methods which are discussed in detail in Chapter 3 Part I. Some of these middle parts are readily available; more common ones, e.g. the C_{10}^-dialdehyde, are manufactured on a ton scale as industrial intermediates for the technical syntheses of β,β-carotene (3) and astaxanthin (406). For the synthesis of unsymmetrical carotenoids, the C_{10}^-dialdehyde can be converted into a monoacetal derivative. The free aldehyde moiety is coupled with one end group, and the intermediate product is deprotected and then combined with the second end group. In these reactions, there are some positions which permit a coupling in high yield [C(9)-C(10) and C(11)-C(12)] and others [C(7)-C(8)] which, for cyclic carotenoids, give products in only low yield because of steric hindrance due to the adjacent methyl groups. The choice of the middle part and its synthesis has become a simple matter today.