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Review

Stereoselective synthesis of monomeric flavonoids

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Abstract

Polyphenolic compounds have recently attracted considerable interest in the field of nutrition, health and medicine. This is the result of the growing body of evidence suggesting that these compounds may act as potent antioxidants and/or modulate key biological pathways in vivo in mammals. Studies aimed at comprehending the intricate principles that govern the chemistry of these important natural products have thus accelerated over the past decade. Prominent amongst these is the ability to synthesize monomeric prototypes with and without ^{13}C- and radio-labeling. Endeavors exploiting the stereoselective syntheses of representative classes of flavonoid monomers are reviewed here.

Keywords: Stereoselective synthesis; Chalcone epoxides; α-Hydroxydihydrochalcones; β-Hydroxydihydrochalcones; Dihydroflavonols; Flavan-3-ols; Flavan-3,4-diols; Isoflavans; Pterocarpans; Epoxidation; Dihydroxylation

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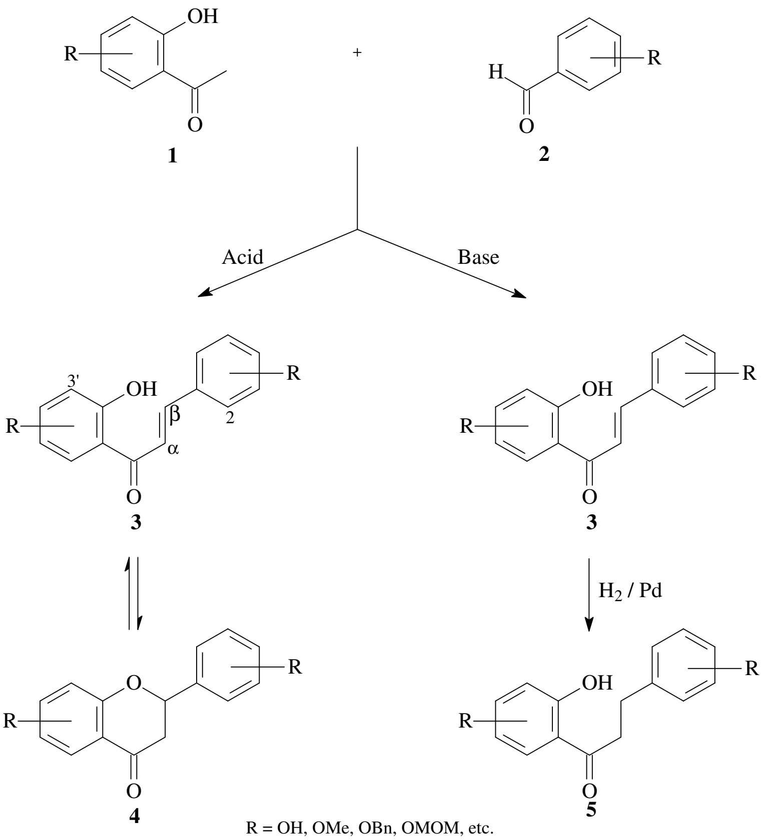
1. Introduction

The study of flavonoid chemistry has emerged, like that of most natural products, from the search for new compounds with useful physiological properties. In addition to the multitude of industrial applications, the oligo- and polymeric proanthocyanidins are now also credited for the profound health-promoting effects of tea, fruit juices and red wine. This is mainly due to their in vitro antioxidant and radical scavenging properties, while the polyflavonoids in red wine have recently been implicated in protection against cardiovascular disorders, e.g., the 'French paradox'. The isolation of the first polymeric proanthocyanidins by Forsyth and Roberts (1960) was followed by the identification of several oligomeric flavonoids in optically active form (Mayer et al., 1966; Drewes et al., 1967; Weinges et al., 1960, 1968; Thompson et al., 1972). Although important progress has been made in the studies of these compounds through acid- (Geissman and Yoshimura, 1966; Haslam, 1974; Fletcher et al., 1977; Botha et al., 1978a, 1981a) or base-catalyzed (Hemingway and Foo, 1983; Foo and Hemingway, 1984) condensation of monomeric units, the systematic study of natural proanthocyanidins is still hampered by the inaccessibility of enantiomeric pure monomeric starting materials. Semisynthetic endeavors of proanthocyanidins are therefore confined to those substitution patterns exhibited by monomeric natural products that are available in quantities sufficient for preparative purposes. Isolation of such compounds often includes tedious processes. In order to alleviate these restrictions, several programs focusing on synthesis of enantiomeric pure flavonoids monomers have been undertaken. However, synthesis of the desired enantiomer in optically pure forms remains a daunting objective and are limited to only a few type of compounds. Chalcone epoxides, α- and β-hydroxydihydrochalcones, dihydroflavonols, flavan-3-ols, flavan-3,4-diols, isoflavans and pterocarpans have thus far been synthesized in reasonable yields and purity.

2. Chalcones, dihydrochalcones and racemic flavanones

Chalcones, and the closely related dihydrochalcones, constitute the most important intermediates in the synthesis of flavonoids and are considered to be the primary C_6–C_3–C_6-precursors to most flavonoids. In general, chalcones are readily accessible via two well established routes which comprise a base-catalyzed aldol condensation or acid mediated aldolization of 2-hydroxyacetophenones **1** and benzaldehydes **2** (Von Konstanecki and Rossbach, 1896; Augustyn et al., 1990a) (Scheme 1). The base-catalyzed aldol condensation represents a



Scheme 1. Acid- and base-catalyzed synthesis of chalcones, racemic flavanones and dihydrochalcones.