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Stereoisomers of Tocopherols
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Rich sources for vitamin-E-active compounds are edible oils originating from plants. Typical examples are shown in the Fig. Sunflower seeds contain \( \alpha \)-tocopherol (1) almost exclusively (Table 1). A mixture of tocopherol homologues (mainly \( \gamma \) and \( \delta \)-tocopherol, 3 and 4) is contained in oil from soybeans, while palm oil has a high concentration of tocotrienols [4]. The industrial importance of this group of compounds is based on their biological and antioxidant activity [5]. The determination of the vitamin E activity by the fetal resorption-gestation test in rats shows that (RRR)-\( \alpha \)-tocopherol (RRR-1) (from Greek: “\( \tau o k o s \)” and “\( \phi r e b o u x \)” which means “to bring forth offspring”) has the highest value of the eight naturally occurring compounds RRR-1–RRR-4 and 5–8) and of the eight stereoisomers of \( \alpha \)-tocopherol [6] (see Table 2). In addition, all tocopherols and tocotrienols function as antioxidants quenching lipid autoxidation reactions.

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**Stereoisomers of Tocopherols – Syntheses and Analytics**

Thomas Netscher*

Abstract. After an introduction summarizing the relevance of vitamin-E-active compounds, a short overview about the work done at Roche (in Basel and Nutley, USA) from the early 1960s to the 1990s is given. Selected research activities of the Basel group during recent years on the synthesis and stereochemical analysis of tocopherols and building blocks are described in more detail.

1. Introduction

Vitamin E is the most important fatsoluble antioxidant. The term vitamin E is recommended to be used as the generic descriptor for all tocopherol and tocotrienol derivatives exhibiting qualitatively the biological activity of \( \alpha \)-tocopherol [1]. The naturally occurring components of this group hitherto discovered are single-isomer products. The \( (2R,4'R,8'R) \)-configuration is found in \( \alpha \)-, \( \beta \)-, \( \gamma \)-, and \( \delta \)-tocopherol (RRR-1–RRR-4), and \( \alpha \)-, \( \beta \)-, \( \gamma \)-, and \( \delta \)-tocotrienol (5–8) possess \( (2R,3'E,7'E) \)-configuration [2][3].

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1. Introduction

Vitamin E is the most important fat-soluble antioxidant. The term vitamin E is recommended to be used as the generic descriptor for all tocopheryl and tocotrienol derivatives exhibiting qualitatively the biological activity of α-tocopherol [1]. The naturally occurring components of this group hitherto discovered are single-isomeric products. The (2R,4′R,8′R)-configuration is found in α-, β-, γ-, and δ-tocopherol (RRR-1–RRR-4), and α-, β-, γ-, and δ-tocotrienol (5–8) possess (2R,3′E,7′E)-configuration [2][3].

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phol (RRR-1) is obtained by enrichment and purification of mixtures of tocopherol homologues (RRR-1-RRR-4) from soybean deodorizer distillates, followed by permethylation (halo- [8], amino- [9], or hydroxalkylation [10] with subsequent reduction, Scheme 2) to RRR-1. The 1500-2000 t per year of this semisynthetic ‘vitamin E from natural sources’ are mainly produced by Henkel and ADM (USA) and Eisai (Japan) [3]. Roche will enter this market in the near future [11]. In contrast, no economic commercial total synthesis of naturally identical (RRR)-α-tocopherol (RRR-1) could be realized so far, despite the rapid advances in stereoselective synthesis and the considerable efforts in approaches to this product [12].

2. Syntheses of Stereoisomeric α-Tocopherols at Roche

The first synthesis of RRR-1 and SRR-1 was published by Mayer et al. in 1963 [13]. The enantiomeric aldehydes S-12/R-12 (derived from trimethylhydroquinone 10 via an optical resolution of quinine salts) were coupled with the phosphonium salt RR-13 (obtained by degradation of natural (2E,7R,11R)-phytol, 11) by a Wittig reaction (Scheme 3). In combination with further investigations, including the inversion of the configuration at C(2) of the chroman ring, the absolute configuration of natural α-tocopherol could be elucidated [14].

Later on, several synthetic schemes have been employed for the stereoselective synthesis of isomers of α-tocopherol, in particular RRR-1 [15][16]. Examples of optically active intermediates prepared and used at Roche are compiled in Scheme 4. Four general strategies were followed. Classical optical resolution delivered mainly chroman building blocks (14-20) [13][17-27]. Microorganisms and enzymes [28] were used for the preparation of intermediates 21-28 [29-37]. Several breakthroughs in enantioselective catalysis like in allylamine → enamine isomerization.

Table 1. Content of Vitamin E Compounds in Refined Vegetable Oils [4]

| Vitamin E Compound | Sunflower Seed [mg per 100 g of oil] | Soybean | Palm |
|--------------------|-------------------------------------|---------|------|
| α-tocopherol       | 59.5                                | 10.99   | 18.32|
| β-tocopherol       | 0                                   | 0       | 0    |
| γ-tocopherol       | 3.54                                | 62.4    | 0    |
| δ-tocopherol       | 0                                   | 20.4    | 0    |
| α-γ-tocotrienol    | 5 + 7                               | 0       | 17.21|

Table 2. Relative Vitamin E Activity: a) of Stereoisomers of α-Tocopheryl Acetate, b) Values of Natural Tocopherols RRR-1 to RRR-4 and Tocotrienols (Determined by the Fetal Resorption-Gestation Test in Rats [6])

| Tocopheryl-Acetate Derivatives | a) | Tocopherols/Tocotrienols | b) |
|--------------------------------|----|-------------------------|----|
| RRR-α                          | 100%| RRR-1 (α)               | 100%|
| RRS-α                          | 90% | RRR-2 (β)               | 57% |
| RSS-α                          | 73% | RRR-3 (γ)               | 31% |
| SSS-α                          | 60% | RRR-4 (δ)               | 1.4%|
| RSR-α                          | 57% |                        |     |
| SRS-α                          | 37% | 5 (α)                   | 30% |
| SRR-α                          | 31% |                        |     |
| SSR-α                          | 21% | concentrate from palm-oil fatty-acid residue | 35-47% |

Figure. Vitamin-E-containing plants (from left): sunflower, soybeans (photos: Keystone, Zürich), and palm tree with fruits (photo: M. Jordi, Roche)
[38–41], hydrogenation [42–44], or Sharpless epoxidation [45] opened the way to a variety of products 29–37 [39][40][44] [46–51] during the last decade.

Chiral auxiliaries in stoichiometric amounts and chiral-pool educts were also applied (11, 38–40) [7][13][23][29][30] [49]. A crucial question in several routes was the stereoselectivity of chemical chroman ring-closure reactions which were investigated in detail [14][52]. The enzymatic cyclization reaction of tocopherol precursor 41 with tocopherol cyclase isolated from anabaena variabilis (bluegreen algae) in the presence of D2O yielded stereospecifically labeled γ-tocopherol derivative 42a (Scheme 5). The methyl ether derivative 42b could be shown to be identical with the product chemically synthesized by two independent routes; in one of them, a highly stereoselective, although low-yield S_N^2 substitution reaction of secondary, oxo-neopentyl-type sulfonates 43 was a key-step [53].

3. Stereochemical Analysis of α-Tocopherol and Side-Chain Building Blocks

In the enantioselective preparation of isoprenoid side-chain building blocks useful in the synthesis of tocopherols and...
4. Recent Stereoselective Syntheses and Analytical Separation of Isomeric Tocopherols

While the preparation of (RRR)-\(\alpha\)-tocopherol (RRR-1) and stereoisomers thereof has been studied extensively, only few reports exist on stereoselective syntheses of other (\(\beta\), \(\gamma\), or \(\delta\)) tocopherols, although (RRR)-\(\gamma\)-tocopherol (RRR-3) is the predominant component of the vitamin E group in most vegetable oils, e.g. from soybean or corn (maize). Mixtures of (2R,4'R,8'R)- and (2S,4'R,8'R)-tocopherols, so-called 2-ambo-tocopherols [1] have been obtained, mainly by acid-catalyzed condensation reactions with natural phytol [11] [7] [63] [64].

The first total syntheses of (RRR)-\(\gamma\)-tocopherol (RRR-3) and (RRR)-\(\delta\)-tocopherol (RRR-4) have recently been realized in our laboratories [65] [66]. When starting from the corresponding hydroquinones 52 (Scheme 8), the glycosyl derivatives 53 were obtained in which the diol function of the carbohydrate moiety served as an anchor for the separation of diastereomeric esters by conventional flash chromatography on silica gel [56]. Triflates 54 [67] [68] were then coupled [69] [70] with hexahydrofarnesyl Grignard reagent 55 [71] to yield tocopherol derivatives 56 in high chemical and stereochemic purity.

By applying the same methodology, several stereoisomers of \(\gamma\) and \(\delta\)-tocopherol were also synthesized which allowed the complete assignment of peaks in the analytical procedure described in the preceding chapter for \(\alpha\)-tocopherol. As a result, the capability of the system for the stereochemical analysis of tocopherols could be improved considerably: all 24 stereoisomers and/or homologues of \(\alpha\), \(\gamma\), and \(\delta\)-tocopherol can now be determined quantitatively by the HPLC-GC method.
