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1. Introduction

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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*)-α-tocopherol (*RRR*-**1**) (from greek: 'τόκος' and 'φέρειν' which means 'to bring forth offspring') has the highest value of the eight naturally occuring compounds *RRR*-**1**–*RRR*-**4** and **5**–**8**) and of the eight stereoisomers of α-tocopherol [6] (see *Table 2*). In addition, all tocopherols and tocotrienols function as antioxidants quenching lipid autoxidation reactions.

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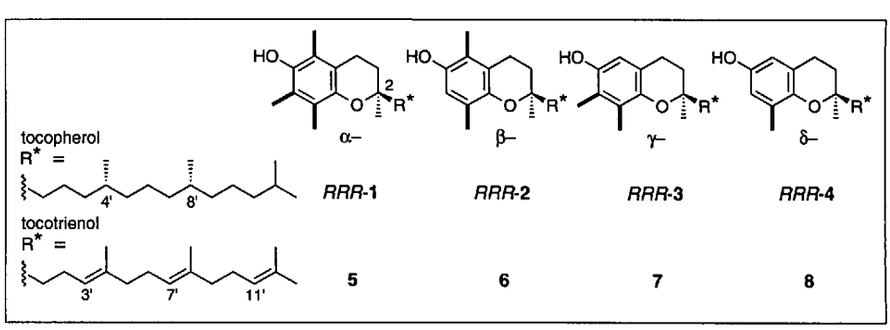

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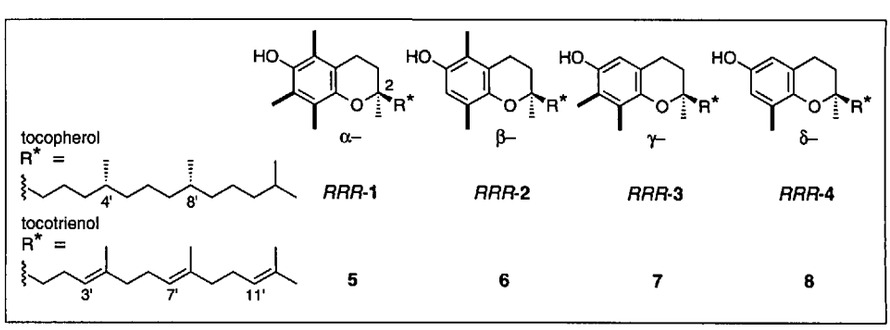

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Figure. *Vitamin-E-containing plants* (from left)*: sunflower, soybeans* (photos: Keystone, Zürich), *and palm tree with fruits* (photo: *M. Jordi, Roche*)

pherol (*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 hydroxyalkylation [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].

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	1	59.5	10.99	18.32
β-tocopherol	2	0	0	0
γ-tocopherol	3	3.54	62.4	0
δ-tocopherol	4	0	20.4	0
α- +γ-tocotrienol	5 + 7	0	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])

a) Tocopheryl-Acetate Derivatives		b) Tocopherols/Tocotrienols	
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%

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 (2*E*,7*R*,11*R*)-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

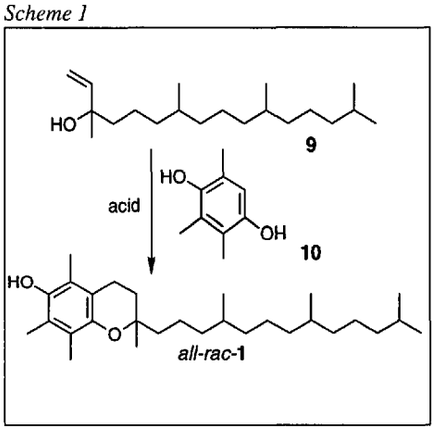
[38–41], hydrogenation [42–44], or *Sharpless* epoxidation [45] opened the way to a variety of products **29–37** [39][40][44] [46–51] during the last decade.

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 D_2O 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 independant routes; in one of them, a highly stereoselective, although low-yield S_N2 substitution reaction of secondary, oxo-neopentyl-type sulfonates **43** was a key-step [53].

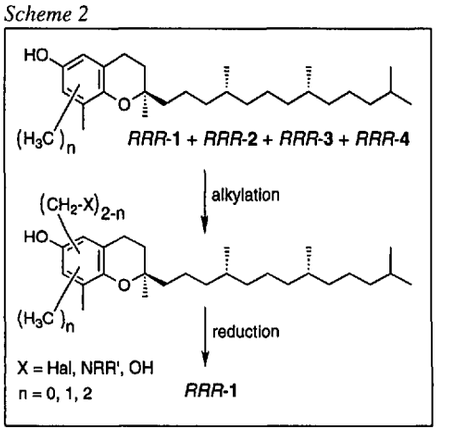
3. Stereochemical Analysis of α-Tocopherol and Side-Chain Building Blocks

In the enantioselective preparation of isoprenoid side-chain building blocks useful in the synthesis of tocopherols and

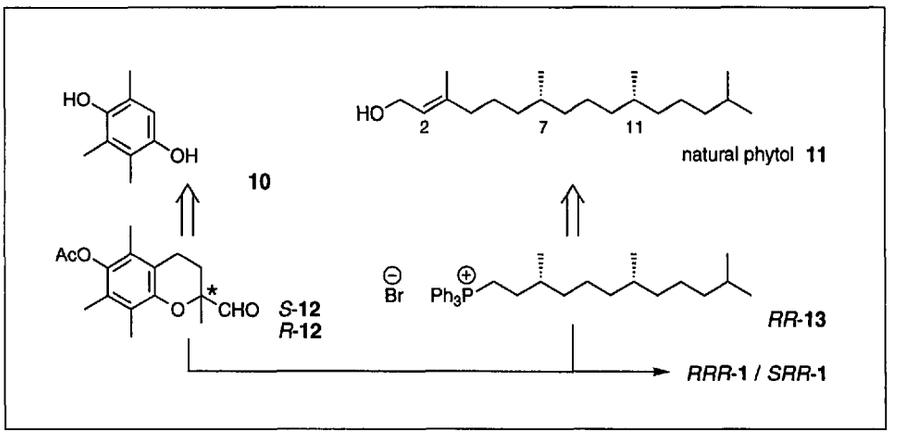
Scheme 1



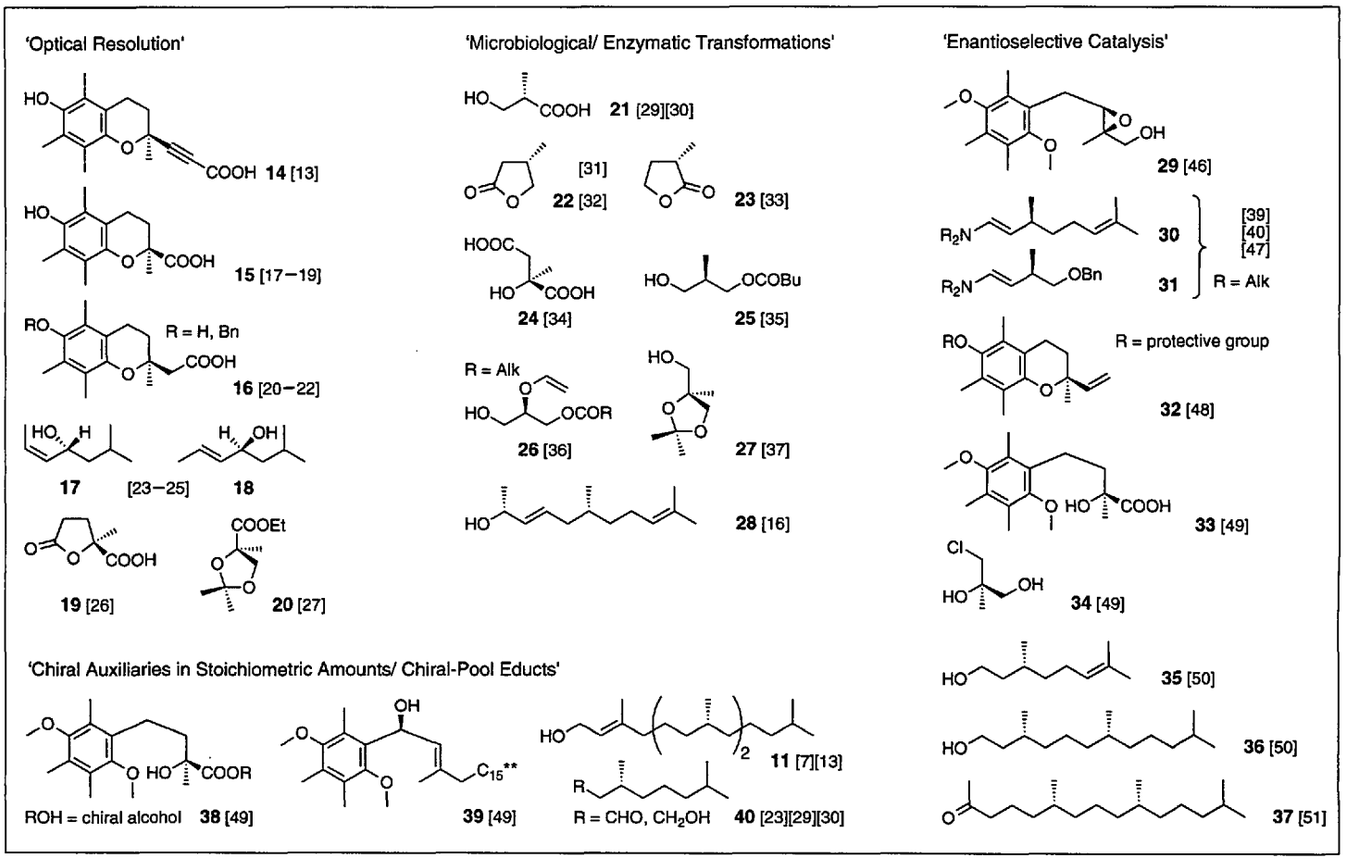
Scheme 2



Scheme 3



Scheme 4



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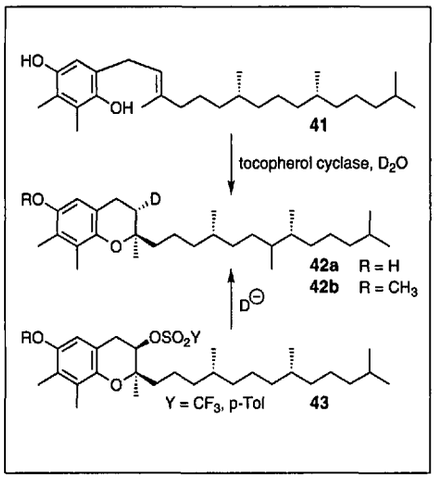
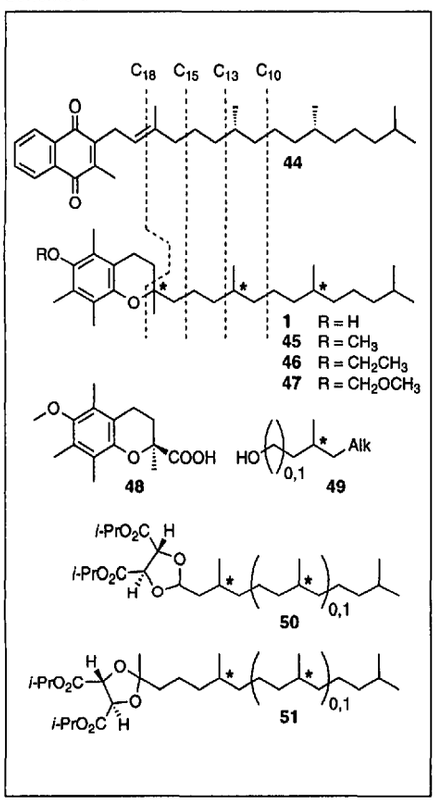
Scheme 5



Scheme 6



(2'*E*,7'*R*,11'*R*)-vitamin K_1 (**44**, *Scheme 6*) reliable analytical methods are required. We have developed procedures for the stereochemical analysis of methyl-branched aliphatic alcohols (*e.g.* C_{10} and C_{15}) and carbonyl compounds (*e.g.* C_{13} and C_{18}). (*S*)-Trolox™ methyl ether (**48**) proved to be a reagent superior to others for the determination of the enantiomeric purity of alcohols **49** by GC or SFC of the corresponding diastereomeric esters [54–57]. Acetals derived from C_2-symmetric tartaric esters allow the simultaneous analysis of two stereogenic centers in aldehydes (→ **50**) and ketones (→ **51**) by capillary gas chromatography [58]. Due to the excellent reproducibility (±0.3%), this method is applicable to the analysis of highly enriched (d.e./e.e. > 95%) samples and is, therefore, a useful tool in optimizing enantioselective reactions, *e.g.* the ruthenium-catalyzed asymmetric hydrogenation [42–44][50][51].

The stereoisomers of α-tocopherol (**1**) do not only show different vitamin E biopotencies as mentioned in the introduction, but also selective biodiscrimination (uptake and distribution) in animal tissues [59]. For these biological as well as chemical investigations the analytical separation and quantification of all eight individual compounds had to be developed. Based on earlier work on the trimethylsilyl and the methyl ether (**45**) derivatives [60], this could be performed by a combination of HPLC on a chiral and GC on an achiral phase (*Scheme 7*) by using the ethyl ether derivative **46** [61]. Further improvements led to a currently routinely used procedure by which quantities as low as 0.1% can be determined [62]. Regarding the determination of all stereoisomers of α-tocopherol by a single operation, it is remarkable that the MOM-ether derivative **47** gave an HPLC elution profile showing seven of eight possible peaks [61].

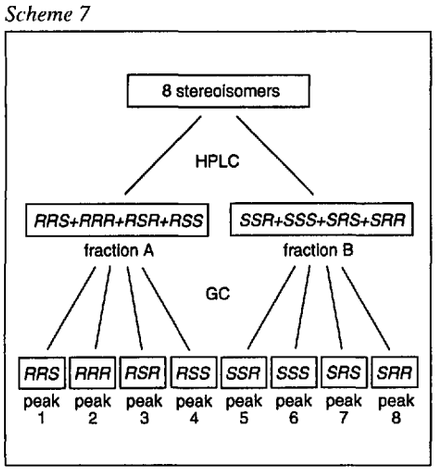
4. Recent Stereoselective Syntheses and Analytical Separation of Isomeric Tocopherols

While the preparation of (*RRR*)-α-tocopherol (*RRR*-**1**) and stereoisomers thereof has been studied extensively, only few reports exist on stereoselective syntheses of other (β-, γ-, or δ-) tocopherols, although (*RRR*)-γ-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 (2*R*,4'*R*,8'*R*)- and (2*S*,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].

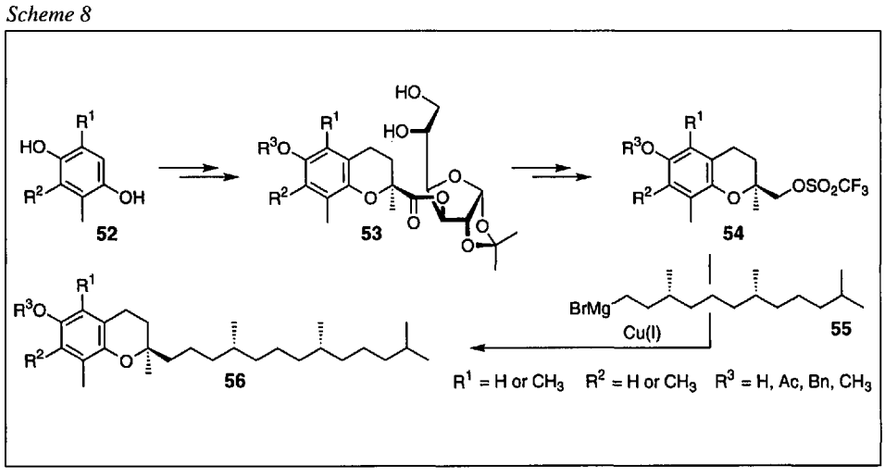
The first total syntheses of (*RRR*)-γ-tocopherol (*RRR*-**3**) and (*RRR*)-δ-tocopherol (*RRR*-**4**) have recently been realized in our laboratories [65][66]. When starting from the corresponding hydroquinones **52** (*Scheme 8*), the glycosyl derivatives **53** were obtained in which the diol function 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 stereochemical purity.

By applying the same methodology, several stereoisomers of γ- and δ-tocopherol were also synthesized which allowed the complete assignment of peaks in the analytical procedure described in the preceeding chapter for α-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 α-, γ-, and δ-tocopherol can now be determined quantitatively by the HPLC-GC method.

Scheme 7



Scheme 8



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