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Building Up Quarternary Stereocenters of Chromans by Asymmetric Redox Organocatalysis: A New Entry to Vitamin E

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Chiral chroman compounds represent an important class of ubiquitous natural products and artificial analogues exhibiting a broad spectrum of biological activities. While synthetic active ingredients are pursued due to their (potential) pharmaceutical applications, vitamin E (consisting of a group of compounds exhibiting a certain biological activity) is of particular interest as a well-known essential nutrient.[1] The component α-tocopherol has been shown to be the most important lipid-soluble radical-chain-breaking antioxidant in living cells suppressing lipid peroxidation.[2a] It is, therefore, of high economic value and has been used on large scale in animal nutrition for several decades. Due to its antioxidant properties (independent of configuration), this product is manufactured on the scale of tens of thousands of tons per year worldwide in the form of the all-racemic equimolar mixture of all eight stereoisomers.

All naturally occurring vitamin E components, however, are single-isomer compounds. The α-, β-, γ-, δ-tocopherols (**1a–d**) possess the 2*R*,4′*R*,8′*R* configuration, and the 2*R*,3′*E*,7′*E* configuration is found in α-, β-, γ-, δ-tocotrienols (**2a–d**) (Figure 1). For the second action of vitamin E, the

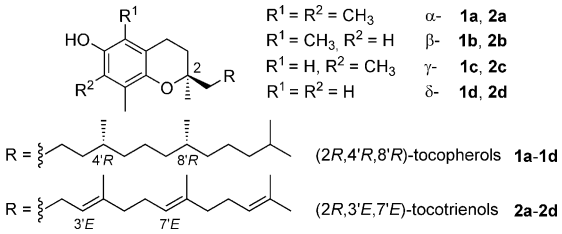

Figure 1. Naturally occurring tocopherols and tocotrienols.

specific vitamin E activity experimentally determined as its essential role in the reproduction of certain animals, chirality is decisive. (2*R*,4′*R*,8′*R*)-α-Tocopherol (**1a**) is the most potent in this respect, while the other stereoisomers show qualitatively the same, but quantitatively lower activity.[2b,c] Industrially, **1a** can be accessed from natural sources only in limited amounts. Therefore, the development of scalable and environmentally as well as economically acceptable procedures for its large-scale synthesis has been of high interest since its first chemical synthesis in the early 1960s.

Although various partial and total syntheses of target compound **1a** based on diverse novel synthetic methodologies have been worked out by several academic and industrial research groups around the world during the past 40 years, none of them could so far fulfill the challenging requirements of an efficient large-scale synthesis. While the highly selective generation of chirality in the aliphatic isoprenoid side chain of tocopherols seems largely solved by the seminal achievements of the groups led by Noyori and Pfaltz in ruthenium- and iridium-catalyzed asymmetric hydrogenation,[3] two other problems remain to be addressed: The diastereo/enantioselective creation of the quarternary chroman stereocenter and the coupling of chroman and side-chain moieties.

Concepts for the simultaneous formation of the chroman framework and coupling with (part of) the side chain were therefore developed by the groups of Trost (asymmetric allylic alkylation)[4] and Tietze (domino Wacker–Heck reaction)[5] both using palladium catalysis. In recent years, organocatalysis has offered novel methods for the stereoselective formation of carbon–carbon and carbon–heteroatom bonds.[6] Woggon and co-workers achieved the simultaneous creation of the tertiary chromanol stereocenter and coupling with the chiral side chain by a domino aldol–oxa-Michael reaction as the organocatalytic key step.[7] These elegant approaches also deliver overall or partial good to excellent selectivities; however, they still suffer from disadvantages such as the laborious preparation of starting materials, multistep downstream chemistry, and high catalyst loading. A completely different approach using metabolic engineering was disclosed by DellaPenna and Shintanie and commented on in a Highlight.[8]

Recently the Ishihara group attracted attention in the field with a conceptual new entry to chiral chroman compounds based on a catalytic metal-free chemoselective oxidative cyclization of monoprotected hydroquinones which proceeded in high yield and optical induction under mild reaction conditions (**3**→**4**, Scheme 1).[9] Key elements of this remarkable transformation are the *N*-phenylimidazol-2-yl (Z)

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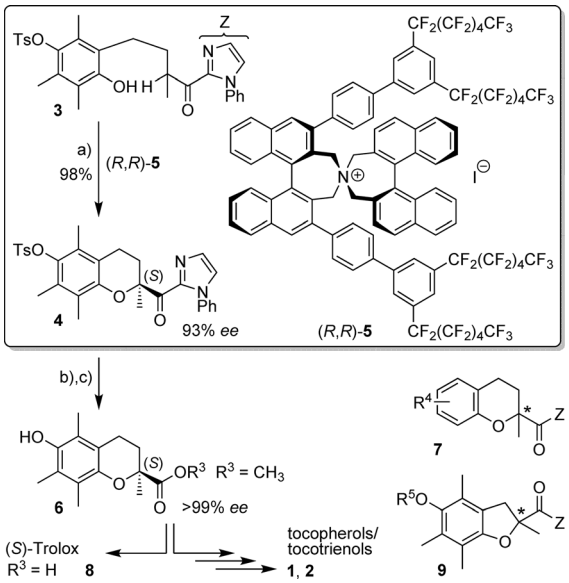
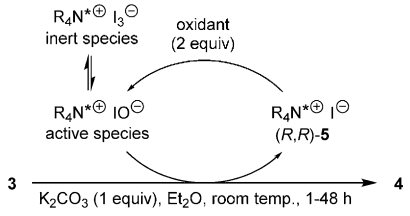


Scheme 1. Asymmetric hypoiodite-catalyzed chroman ring closure. a) Cumene hydroperoxide (2 equiv), K_2CO_3 (1 equiv), Et_2O, (*R*,*R*)-**5** (1 mol%), 25 °C, 10 h; b) MeOTf (5 equiv), CH_2Cl_2, 25 °C, 1 h, then DBU (1.2 equiv), MeOH, 25 °C, 1 h, then recrystallization (hexane/EtOAc); c) Mg (10 equiv), MeOH, 25 °C, 2 h; Ts = *para*-toluenesulfonyl, Tf = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

group as an auxiliary at the γ-(2-hydroxyphenyl)ketone moiety, protection of the remote phenolic hydroxy group of the hydroquinone as a sulfonic ester, the stoichiometric use of an alkyl hydroperoxide in combination with an inorganic base, and the catalysis induced by 0.05–10 mol% of a chiral ammonium iodide based on a binaphthyl structural motif in an aliphatic ether (*tert*-butyl methyl ether or, preferably, diethyl ether) as the solvent.

During the investigation, several difficulties had to be overcome. The OTs (O-*para*-toluenesulfonyl) group proved to be sufficiently stable towards the oxidative conditions while the initially used *tert*-butyldimethylsilyl ether was oxidized to dearomatized quinone and peroxyquinol side products. Generally, the weak oxidant cumene hydroperoxide was superior to *tert*-butyl hydroperoxide and 30% aqueous hydrogen peroxide. According to detailed mechanistic investigations of the catalytic cycle (Scheme 2) the presence of potassium carbonate (1 equiv) was essential to suppress the formation of the inactive I_3^- species, which can be transformed (back) to the catalytically active IO^- salt by alkaline hydrolysis. Indeed no conversion was detected at low catalyst



Scheme 2. Proposed catalytic cycle for enantioselective cyclization.

concentration without base. Optimization of the substitution pattern of the Maruoka-type chiral ammonium precatalysts[10] showed that best enantioselectivities were achieved with perfluoroalkyl-containing substituted binaphthyl units.

Under optimized conditions cycloetherification of precursor **3** in the presence of 1 mol% (*R*,*R*)-**5** yielded (*S*)-chroman derivative **4** in 98% yield and 93% *ee*, and it was further transformed to intermediate **6** (Scheme 1). The syntheses of (*S*)-Trolox (**8**), (2*R*,4′*R*,8′*R*)-α-tocopherol (**1a**), and (2*R*,3′*E*,7′*E*)-α-tocotrienol (**2a**) were completed by using established methods. Also differently substituted chroman building blocks **7** could be obtained analogously with *ee* values of 85–93% and they served as intermediates in the syntheses of the homologous β-, γ-, and δ-tocopherols (**1b–d**) as well as several structurally related pharmaceuticals. The catalyst turnover numbers (TONs) of up to 200 (loading of 0.5 mol%) are notably high for such transformations, and a TON value of 2000 (corresponding to a loading of 0.05 mol%) was reported for a catalyst structurally closely related to (*R*,*R*)-**5** in the much faster cyclization of a corresponding β-(2-hydroxyphenyl)ketone to five-membered benzofuran **9** (R^5 = Ts).

Without a doubt this work belongs to the most innovative approaches for the enantioselective preparation of the chroman (and benzofuran) skeleton in the past few years and represents a considerable step forward in the field. Nevertheless, some limitations at the current status should be mentioned. Starting material **3** contains both a large auxiliary (Z) and protective (Ts) group, and is (currently) prepared in six steps from commercially available materials. The synthesis of the phase-transfer catalyst also requires multiple steps. Although the 1 mol% loading of (*R*,*R*)-**5** is already rather low, it still corresponds to a high weight proportion since the catalyst contains 52 fluorine atoms and has a molecular mass exceeding 2000. The impressive but still insufficient level of stereoselectivity (up to 93% *ee*) must be increased by recrystallization, and additional manipulations in downstream chemistry are required to arrive at the target product(s). Finally, the new methodology can offer "only" a possible solution for the generation of the chiral chroman core structure.

In commentaries on the contribution of the Nagoya research group,[9b,c] discussions have been started on whether this work is a low-cost and "green" synthesis method for making tocopherols, and whether this route can compete with work published earlier. It must be clearly stated that no simple and precise answer regarding a practical, that is, commercially viable solution is apparent. In general, the overall route to a product has to fulfill all requirements in terms of cost and environmental sustainability. It is known from experience that considerable effort in process research and development is necessary to translate a scientific breakthrough into a large-scale process. This concerns not only the number of steps, yields, and selectivities, but also issues such as availability, stability, and recyclability of auxiliaries, reagents, catalysts, and solvents, energy consumption, and waste formation. Often catalyst activity and productivity become major challenges and determine whether a process is economical.

The excellent results described should also be applicable to the search for new drug candidates not easily accessible by other methods. Despite the limitations mentioned, it is remarkable that this new type of redox catalysis representing a fundamentally novel concept could be elaborated in the field of already advanced enantioselective synthesis, and organocatalysis in particular. The future will show which (combinations of) highly sophisticated methods of asymmetric catalysis with and without metals can contribute to environmentally benign and economically feasible processes for the efficient preparation of such complex biologically active compounds.

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