On the Mechanism of the Acid-Catalyzed Stereoselective Chroman Cyclization Reaction

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Naturally occurring tocopherols and tocotrienols are single-isomer vitamin E compounds. (2R,4'R,8'R)-α-Tocopherol (4) as a prominent example is of high commercial interest due to its biological and antioxidant properties.[1] Although the stereospecific cyclization reaction of intermediates and precursors such as 1a/2a to chromans 3/4 under carefully controlled acidic conditions (Scheme 1) is known for a long time[2,3] and has been used as a key step in many total syntheses,[1,4] the mechanism of this transformation is unknown.

Scheme 1. Stereospecific acid-catalyzed chroman ring formation.

Several proposals are documented in literature. The Roche Nutley research group favoured a chroman ring formation via a hemiketal followed by rearomatization (Scheme 2) or, alternatively, a cyclization via a redox process (Scheme 3).[3] Chroman ring formation by double inversion (Schemes 4 and 5) was also postulated.[5,6]

Scheme 2. Chroman ring formation via hemiketal.[3]
We investigated the course of the acid catalyzed ring closure reaction by starting from doubly \textsuperscript{18}O-labelled derivative \textit{1b} (synthesized via stereoselective bishydroxylation). Chromans 3 and 4 (via intermediate \textit{2b}) obtained by applying standard literature procedures\cite{4,7} showed complete (>95%) chirality transfer as well as \textsuperscript{18}O-incorporation (Scheme 6). Loss of the tertiary hydroxy group and double-inversion as sketched in Schemes 4 and 5 can be ruled out.
Scheme 6. $^{18}$O-Labeling experiments in acid-catalyzed chroman ring formation.

The results of this study corroborate the mechanistic pathway of this key reaction applied in various total syntheses of optically active vitamin E compounds such as $(2R,4'R,8'R)$-$\alpha$-tocopherol (4) and other stereoisomers.

References: