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

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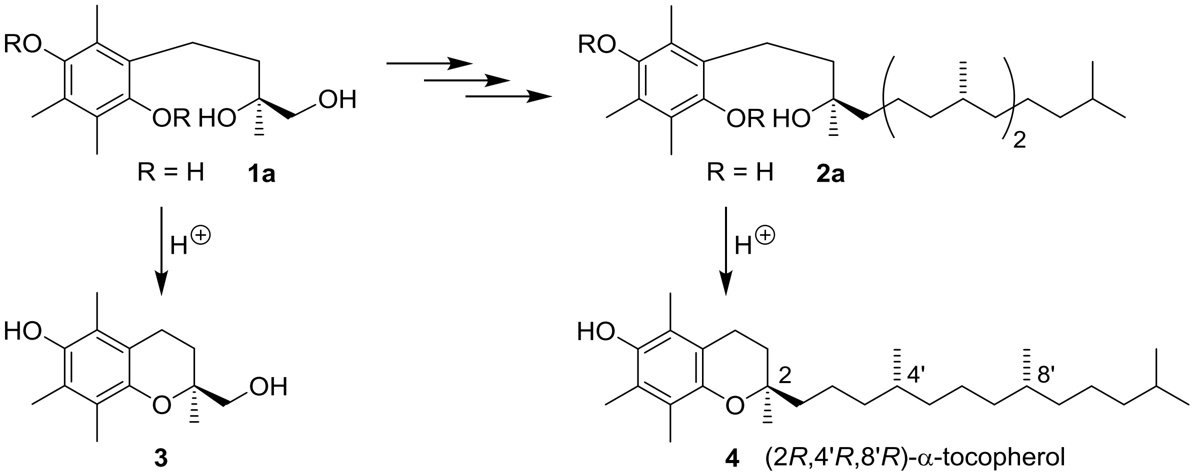
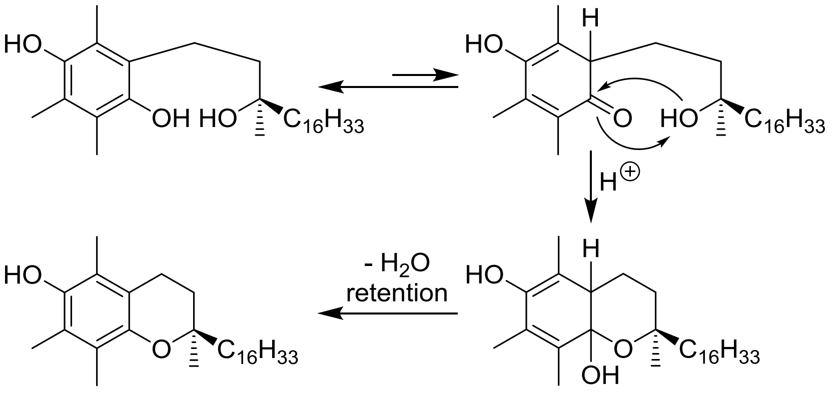
Naturally occurring tocopherols and tocotrienols are single-isomer vitamin E compounds. (2*R*,4'*R*,8'*R*)-α-Tocopherol (**4**) as a prominent example is of high commercial interest due to its biological and antioxidant properties.[1] Although the stereospecific cyclization reaction of intermediates 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.

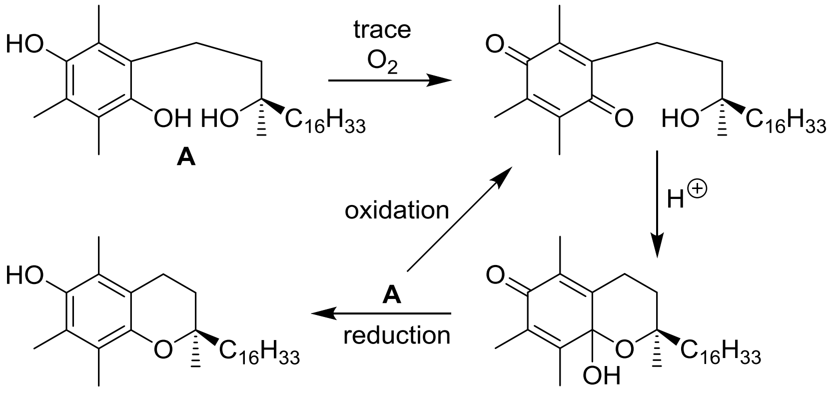


Scheme 1. Stereospecific acid-catalyzed chroman ring formation.

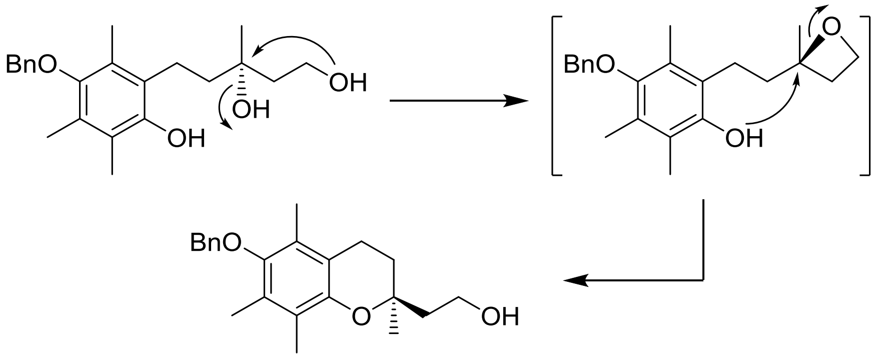
Several proposals are documented in literature. The Roche Nutley research group favoured a chroman ring formation via a hemiketal followed by rearomatization (**Scheme 2**) or, alternatively, a cyclization via a redox process (**Scheme 3**).[3] Chroman ring formation by double inversion (**Schemes 4**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



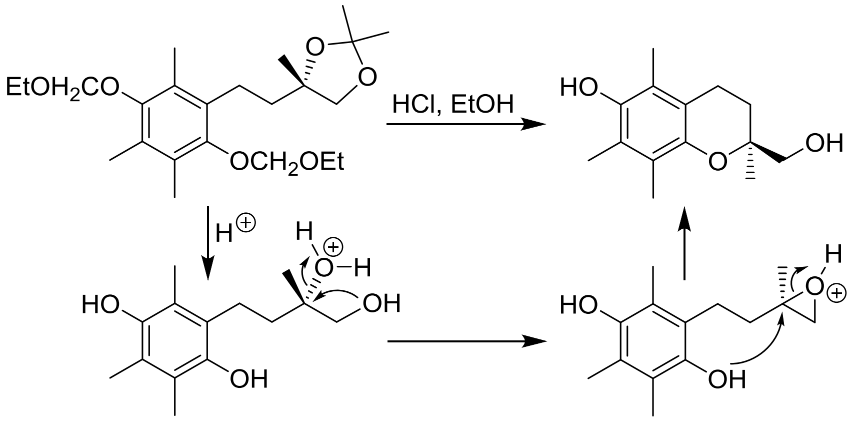
Scheme 2. Chroman ring formation via hemiketal.[3]



Scheme 3. Chroman ring formation via redox cyclization.[3]

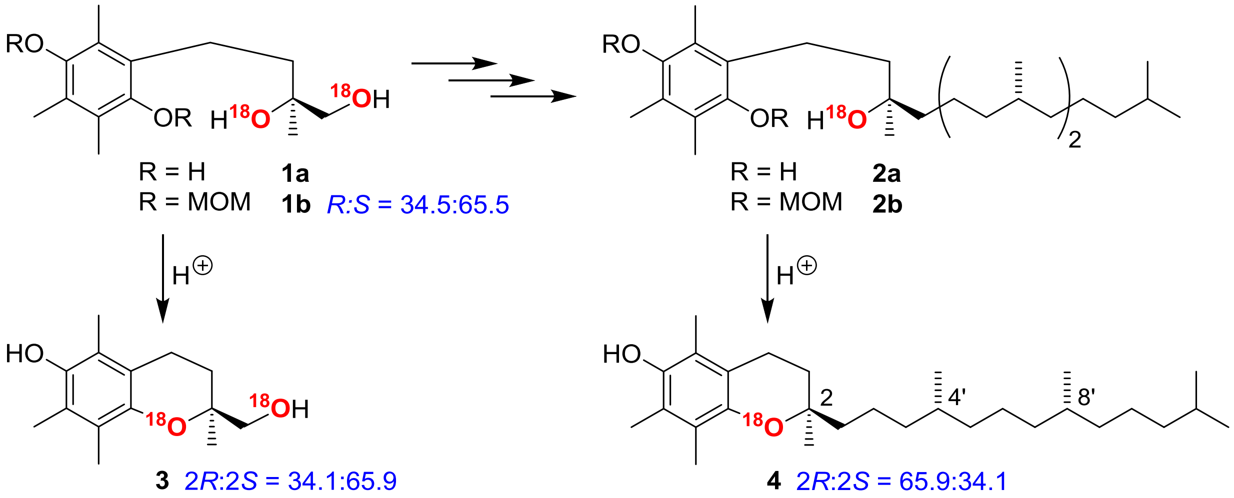


Scheme 4. Proposed chroman ring formation by double inversion.[5]



Scheme 5. Proposed chroman ring formation via epoxide.[6]

We investigated the course of the acid catalyzed ring closure reaction by starting from doubly ^{18}O-labelled derivative **1b** (synthesized via stereoselective bishydroxylation). Chromans **3** and **4** (via intermediate **2b**) obtained by applying standard literature procedures[4,7] showed complete (>95%) chirality transfer as well as ^{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-Labelling 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 (2*R*,4'*R*,8'*R*)-α-tocopherol (**4**) and other stereoisomers.

References:

[1] T. Netscher, *Vitam. Horm.* **2007**, *76*, 155-202; M. Eggersdorfer, D. Laudert, U. Létinois, T. McClymont, J. Medlock, T. Netscher, W. Bonrath, *Angew. Chem. Int. Ed.* **2012**, *51*, 12960-12990. [2] H. Mayer, W. Vetter, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *50*, 1168-1178. [3] N. Cohen, R. J. Lopresti, C. Neukom, *J. Org. Chem.* **1981**, *46*, 2445-2450. [4] See e.g. C. Rein, P. Demel, R. A. Outten, T. Netscher, B. Breit, *Angew. Chem. Int. Ed.* **2007**, *46*, 8670-8673, and references cited therein. [5] E. Mizuguchi, K. Achiwa, *Synlett* **1995**, 1255-1256. [6] H.C. Shen, *Tetrahedron* **2009**, *65*, 3931-3952. [7] J. Hübscher, R. Barner, *Helv. Chim. Acta* **1990**, *73*, 1068-1086.