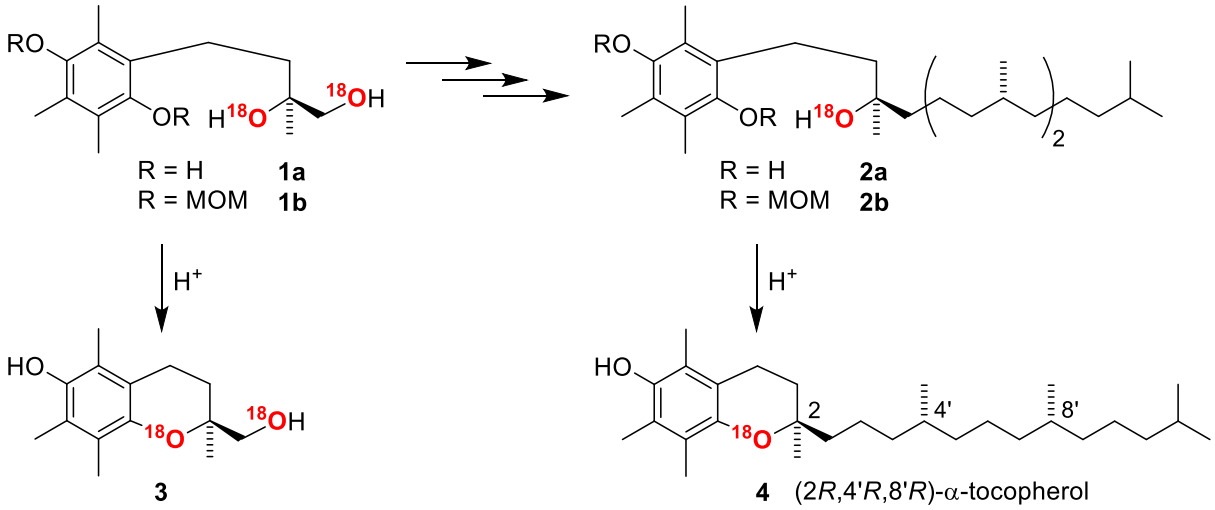
On the Mechanism of the Acid-Catalyzed Stereoselective Chroman Cyclization Reaction

Thomas Netscher, Ann-Christine Loesche

Research and Development, DSM Nutritional Products, P.O. Box 2676,
CH-4002 Basel, Switzerland; thomas.netscher@dsm.com

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 is known for a long time,[2] the mechanism of this transformation is unknown. This acid-catalyzed chroman cyclization has been used as a key step in many total syntheses,[3] and is of importance for larger-scale applications towards vitamin E and corresponding building blocks.



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 showed complete (>95%) chirality transfer as well as ^{18}O-incorporation. The mechanism proposed will be discussed in comparison to findings documented in previous research papers.

[1] T. Netscher, *Vitamins Hormones* **2007**, *76*, 155-202.
[2] H. Mayer, W. Vetter, J. Metzger, R. Rüegg, O. Isler, *Helv. Chim. Acta* **1963**, *50*, 1168-1178; N. Cohen, R. J. Lopresti, C. Neukom, *J. Org. Chem.* **1981**, *46*, 2445-2450.
[3] 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.