TOTAL SYNTHESIS OF α-TOCOPHEROL THROUGH ENANTIOSELECTIVE IRIDIUM-CATALYZED FRAGMENTATION OF A SPIRO-CYCLOBUTANOL INTERMEDIATE

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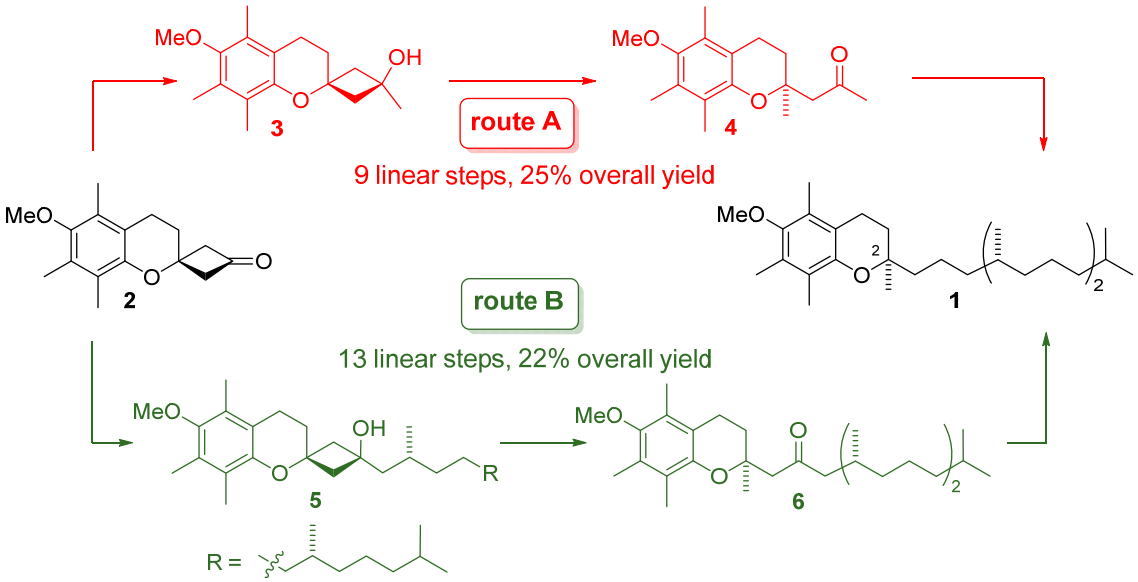
The stereo-controlled synthesis of α-tocopherol, i.e. "Vitamin E", especially with respect to the quaternary stereocenter at C-2 remains a challenging task. In this context we developed a conceptually novel strategy based on an unprecedented iridium-catalyzed "desymmetrizative" fragmentation of spiro-cyclobutanol intermediates.[1]

Starting from the readily available cyclobutanone **2**, two routes towards α-tocopherol methyl ether (**1**) were elaborated. In route A, the Ir-catalyzed key step (employing (*S*)-DTBM-SegPhos as a chiral ligand) afforded ketone **4** with high enantioselectivity (e.r. 97:3). The side chain was then attached via cross metathesis.



In an alternative approach (route B), the side chain was first introduced in a sequence of enyne metathesis and 1,4-hydrogenation.[2] After Pfaltz-hydrogenation of the resulting threefold-substituted olefin, the "late-stage" asymmetric Ir-catalyzed cyclobutanol opening proceeded with even better stereoselectivity to give ketone **6** (d.r. >99:1).

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[1] (a) F. Ratsch, W. Schlundt, D. Albat, A. Zimmer, J.-M. Neudörfl, T. Netscher, H.-G. Schmalz, *Chem. Eur. J.* **2019**, *25*, 4941-4945; for related Rh-catalyzed cyclobutanol fragmentation, see: b) T. Seiser, N. Cramer, *J. Am. Chem. Soc.* **2010**, *132*, 5340-5341, c) L. Souillart, N. Cramer, *Chem. Rev.* **2015**, *115*, 9410-9464.

[2] F. Ratsch, H.-G. Schmalz, *Synlett* **2018**, *29*, 785-792.