

Recent Biomimetic and Organocatalytic Syntheses of α -Tocopherol

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Abstract: We report here on our efforts to develop new strategies for the synthesis of α -tocopherol, the biological most significant member of the vitamin E family. This review comprises five new methods to generate the chiral chromane of α -tocopherol with overall up to 29% yield from commercially available material and up to 94% *de*.

Keywords: Chromane · Enantioselectivity · α -Tocopherol · Tocopherol cyclase · Vitamin E

1. Introduction

Vitamin E comprises tocopherols **1–4** and tocotrienols **5–8** which can be isolated from all photosynthetic organisms (Fig. 1). These compounds exhibit various physiologically significant properties such as the modulation of signal transduction,^[1] anti-inflammatory action^[2] and antioxidant reactivity.^[3]

α -Tocopherol (**1**) is the biologically most important member of the vitamin E family as it acts as the best radical chain-breaking antioxidant in tissues^[4] and binds selectively to a transport protein^[5] providing efficient bioavailability. The antioxidant reactivity of the chromanol system has been investigated in detail^[3] and is attributed to stereoelectronic factors, *i.e.* the lone pair of O(1) is favorably oriented to stabilize the tocopheryl radical **9** produced by homolysis of the phenolic OH group (Scheme 1).

The isolation of pure **1** from natural sources is quite difficult because the compound appears in various amounts along with other vitamin E chromanols.

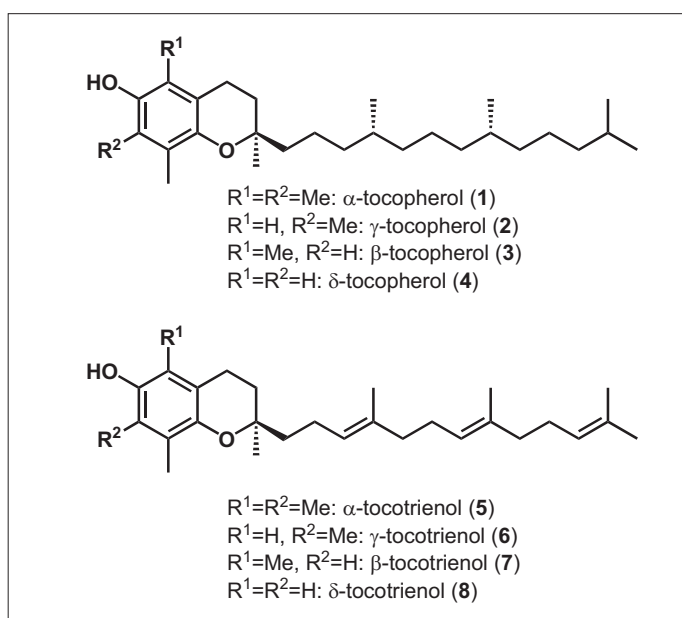
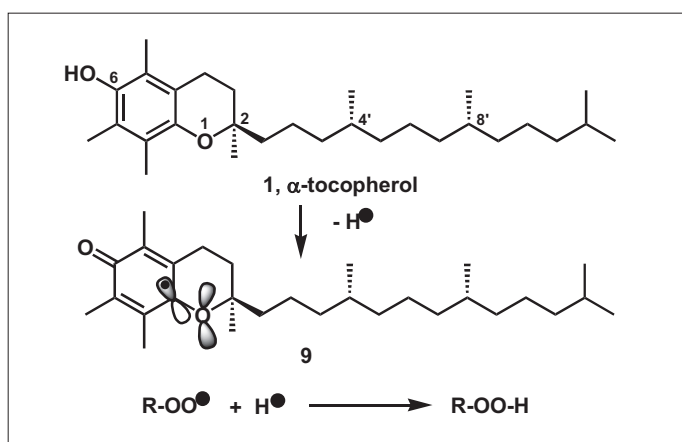


Fig. 1. Structures of vitamin E compounds.



Scheme 1. Antioxidant reactivity of **1**: Formation of tocopheryl radicals such as **9** and trapping of peroxy radicals ROO^{\bullet} that are produced under oxidative stress in membranes for example.

The challenge to prepare chiral **1** results from the presence of stereogenic centers at C(2), C(4'), and C(8'). A comprehensive review by Netscher describes the syntheses of racemic and enantiomerically enriched tocopherols up to 2006.^[6] Since then we have developed several new approaches to chiral chromanols that are reviewed here.

2. Results and Discussion

2.1 Biomimetic Synthesis of α -Tocopherol and α -Tocotrienol

The discovery of the enzyme tocopherol cyclase from *Cyanobacteria*^[7] and investigations of the substrate specificity^[8] and reaction mechanism^[9] revealed that i) the enzyme cyclizes hydroquinone

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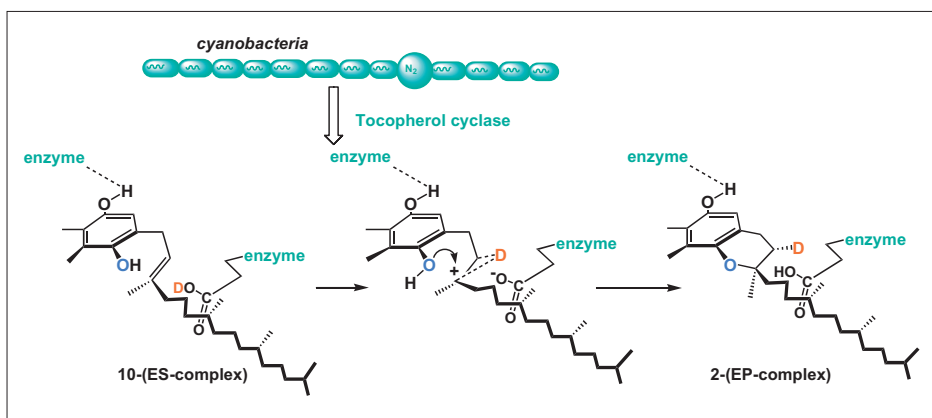
precursors with chiral and unsaturated side chains leading to **2** and **6**, respectively, with the comparable efficiency; and ii) the very hydrophobic 42 kD protein operates by *si* protonation of the double bond and concomitant *re* attack of the phenol (Scheme 2).

In view of the weak acidity of amino acids available in the active site of the protein it was suggested^[10] that substrates such as **10** bind to the enzyme in a high energy conformation (Scheme 2) in which both phenol and proton source are in binding distance of the double bond. This insight led to a biomimetic synthesis of α -tocopherol (**1**) using a large protecting group R and a dipeptide as steric constraints to generate a suitable conformation of the hydroquinone and providing a proton source,^[11] see **11** (Scheme 3).

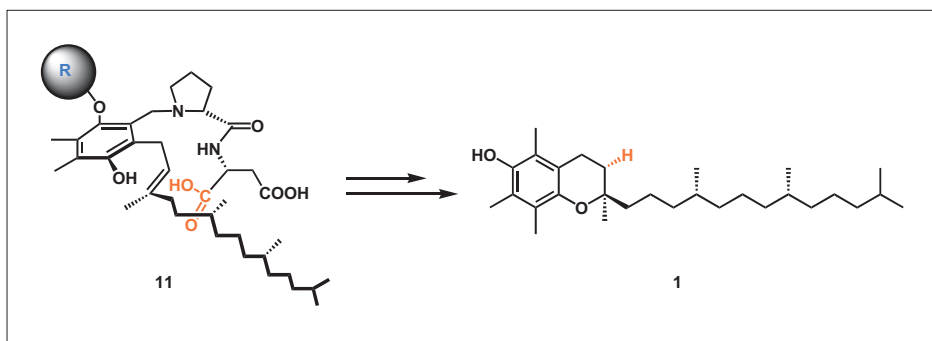
The general strategy to obtain a suitable precursor for cyclization to the chromanol system of vitamin E is outlined in Fig. 2. It was anticipated that cyclization would proceed with the chiral side chain leading directly to **1** as well as with the unsaturated side chain yielding α -tocotrienol (**5**) that could be enantioselectively hydrogenated to **1** using established methods.^[11]

Accordingly, the synthesis of **1** started with the monoprotected hydroquinone **13** which underwent a Mannich reaction with the proline derivative **14** (Scheme 4),^[12] Subsequent esterification with camphanoyl chloride and deprotection gave **15** to which the protected aspartate **16** was added. The resulting phytyl phenol **17** was cyclized in the presence of pTsoH and furnished the protected chromanol dipeptide **18** in excellent yield. The benzylic amine of **18** was removed by hydrogenation and the (2*R*,4'*R*,8'*R*)-tocopherylester **19a** obtained displaying 70% *de* (diastereomeric excess). Systematic investigation of the cyclization reaction revealed that i) the *de* is independent of the camphanoyl unit (useful for *de* determination of the final product), ii) the *de* depends on the chirality of the dipeptide. For example if (*S*)-proline/(*S*)-aspartate were employed the (2*S*,4'*R*,8'*R*)-tocopheryl camphanate was obtained displaying 80% *de*. A similar reaction sequence was used to yield α -tocotrienyl acetate (**20**, 65% *de*) which was subsequently hydrogenated to **19b** in the presence of the catalyst **21**.^[11]

The conversion of hydroquinone precursors such as **17** to chromanols gave surprisingly high *de* values given the fact that the flexibly attached dipeptide is the only chirality inducing unit. To a certain extent this result validates the proposal that in the active site of tocopherol cyclase a high energy conformer of the phytylhydroquinone can cyclize even in the presence of weak acids.



Scheme 2. Reaction mechanism of tocopherol cyclase.



Scheme 3. Biomimetic approach to α -tocopherol (**1**).

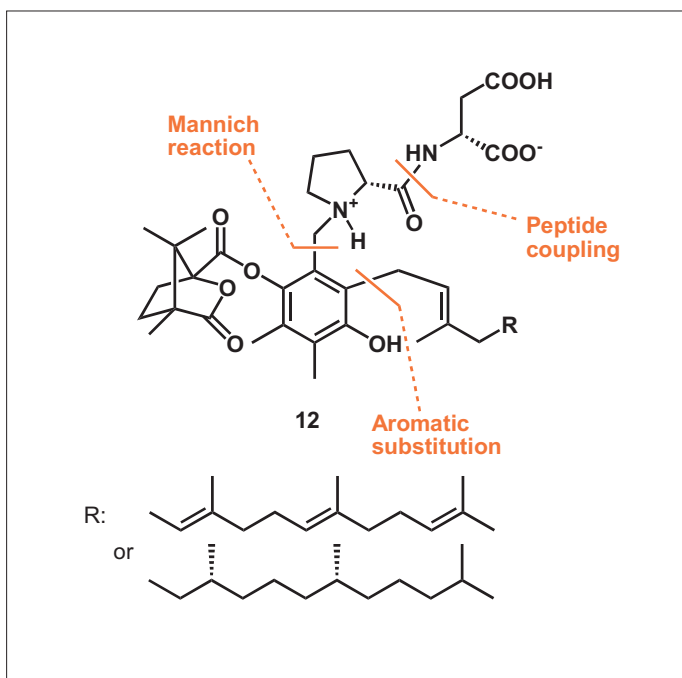


Fig. 2. Retrosynthetic analysis to generate the allylic phenol **12** for cyclization.

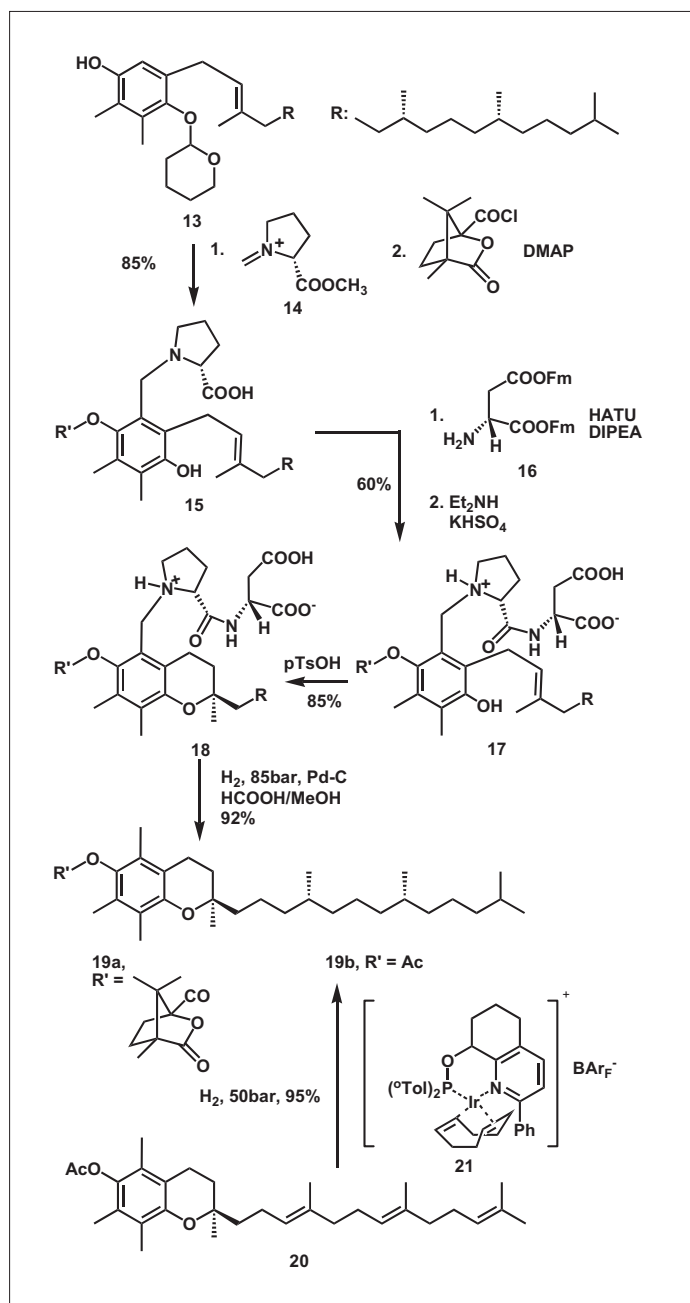
2.2 Organocatalytic Keysteps for the Synthesis of Chromanols

2.2.1 Organocatalysis Using Chiral Dioxetans

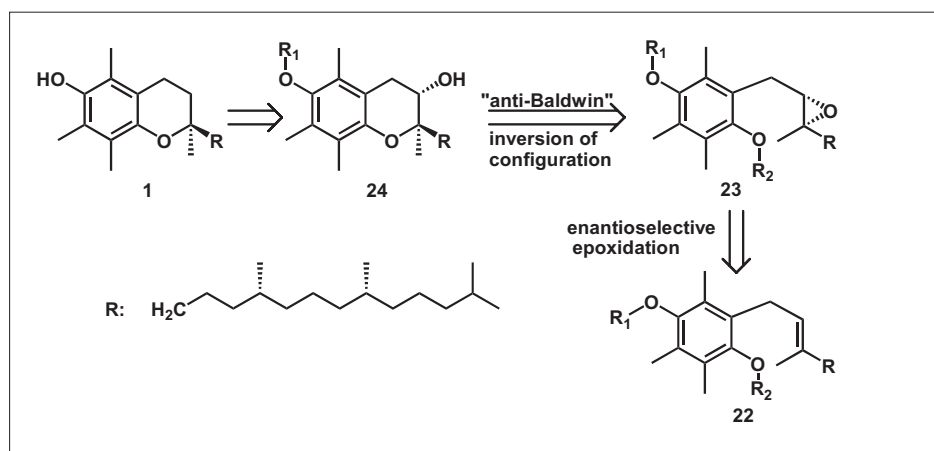
The retrosynthetic plan of this approach to α -tocopherol (**1**) is depicted in Scheme 5. The sequence poses two problems: i) enantioselective epoxidation of a triply substituted double bond lacking ad-

acent functionalization, see **22**, and ii) regioselective, 'anti-Baldwin' ring opening of the epoxide **23** to form the 6-membered chromane system **24** without racemization.

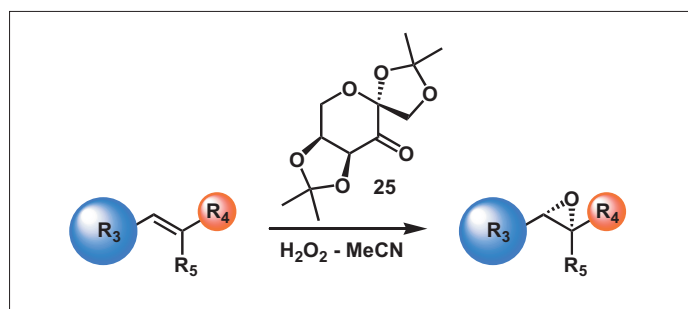
Regarding enantioselective epoxidation we considered the application of organocatalysts developed by Zhao and Shi.^[13] This group has reported that fructose-derived compounds such as **25** (+ H₂O₂) cata-



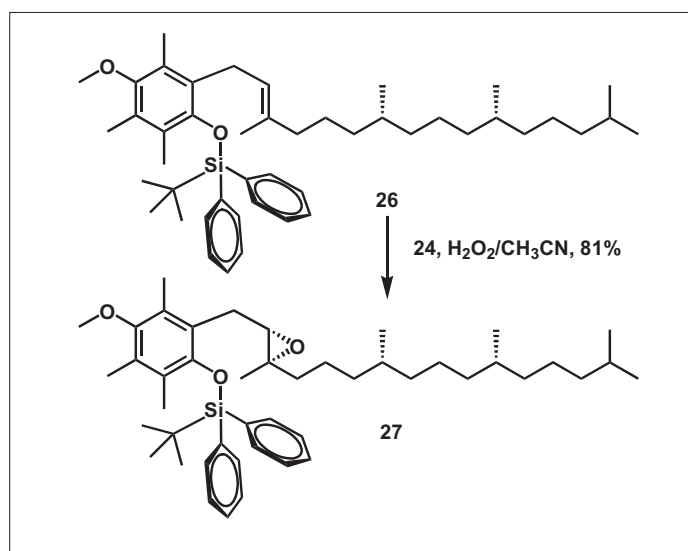
Scheme 4. Biomimetic synthesis of α -tocopheryl- and α -tocotrienyl esters.



Scheme 5. Retrosynthesis in order to obtain chiral chromanols *via* regioselective epoxide ring opening.



Scheme 6. Chiral dioxetanes generated from ketones such as **25** epoxidizing non-functionalized olefins.

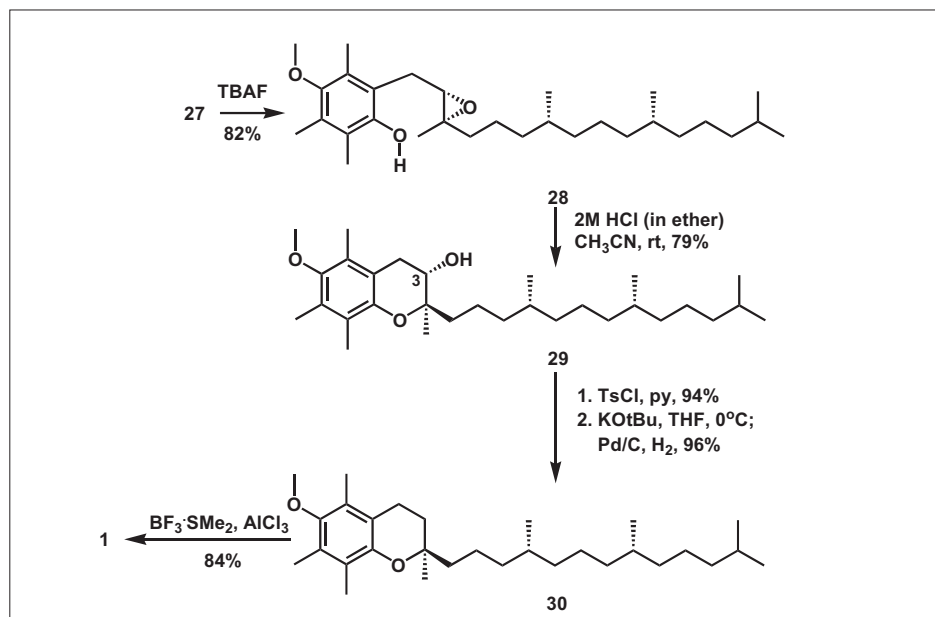
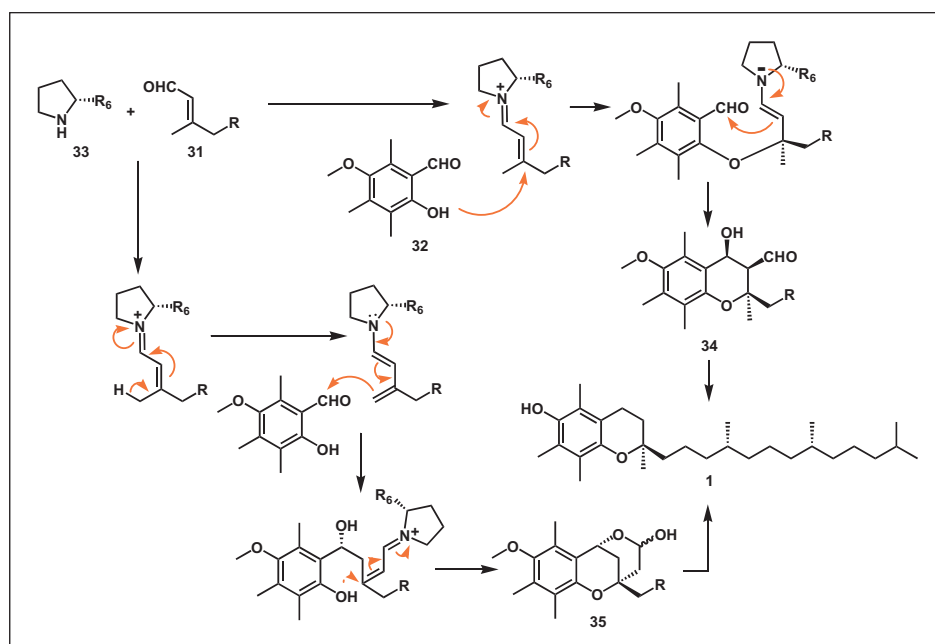


Scheme 7. Diastereoselective 'Shi-epoxidation'.

lyze the formation of chiral epoxides provided the olefin contains groups R_3 and R_4 that are very different in size (Scheme 6).

In principle this is not the case for olefin **22** as both groups adjacent to the double are CH_2 . Nevertheless, we believed we could optimize the substrate through the substituents at the hydroquinone. Screening substrates with nine variations for R_1/R_2 we found one outstanding result for **26** which gave epoxide **27** in 81% yield and 97% *de* (Scheme 7).

In order to accomplish the formation of the chromane system under inversion of configuration we first used conditions reported by Vilotijevic and Jamison^[14] which favored pyran products in MeOH. However, a mono-protected epoxyphytyl hydroquinone gave exclusively the furan product following Baldwin's rule.^[15] A systematic investigation (21 experiments) of the epoxide ring opening finally revealed that the epoxide **28** could be cyclized in acetonitrile/2M HCl-ether to the 3-hydroxy chromane **29** in 79% yield (Scheme 8). Removal of the hydroxyl group went smoothly through the corresponding tosylate, easily eliminated

Scheme 8. Chromanol formation through 'anti-Baldwin' ring opening of epoxide **28**.Scheme 9. Proline-catalyzed domino-aldol-oxa-Michael reaction of phytal (**31**) and salicylaldehyde **32**.

and directly hydrogenated to afford **30** in almost quantitative yield and 93% *de*. Note that the small decrease of *de* from **27** to **30** is due to the extent of carbenium ion formation during the conversion of **28** to **29**. Deprotection of **30** to **1** was accomplished by means of $\text{BF}_3\cdot\text{SMe}_2/\text{AlCl}_3$ without epimerization at C(2).

2.2.2 Organocatalysis Using Proline Derivatives

In recent years organocatalysts derived from proline have been successfully applied for aldol and Mannich reactions.^[16] We considered that a domino-aldol-oxa-Michael reaction between phytal **31** and

salicylaldehyde **32** catalyzed by **33** for example would either give aldehyde **34** or lactol **35** or a mixture of both (Scheme 9). From both intermediates one could envisage preparing α -tocopherol (**1**) by removal of the OH and CHO substituents at the heterocycle. Screening of ten different proline organocatalysts for the reaction between **31** and **32** revealed that **36** (Scheme 10) was the best choice to obtain lactol **35** in 60% yield and 97% *de*; the enantiomer of **36** gave the diastomeric lactol.^[17]

The lactol **35** was oxidized to the benzylic lactone **37** which was readily hydrogenated to afford the acid **38**. Only two further steps, *i.e.* removal of one carbon and de-

methylation, are required to convert the key intermediate **38** into α -tocopherol (Scheme 10). However conditions had to be carefully tuned to prevent racemization at C(2) due to thermal or acid-catalyzed ring opening/ring closure of the chromane system. Finally two procedures were found for the chain cleavage at C(2). Reduction of the acid **38** followed by oxidation gave the aldehyde **39** in 75% yield. Subsequent Rh-catalyzed decarbonylation^[18] furnished the tocopherol ether **30** in 80% yield, 93% *de*. The same compound was obtained from **38** in 72% yield, 94% *de* using a Barton decarboxylation procedure.^[19] Ether cleavage was accomplished by treating **30** with $\text{BF}_3\cdot\text{Me}_2\text{S}/\text{AlCl}_3$; α -tocopherol (**1**) was obtained in 84% yield under retention of configuration at C(2).

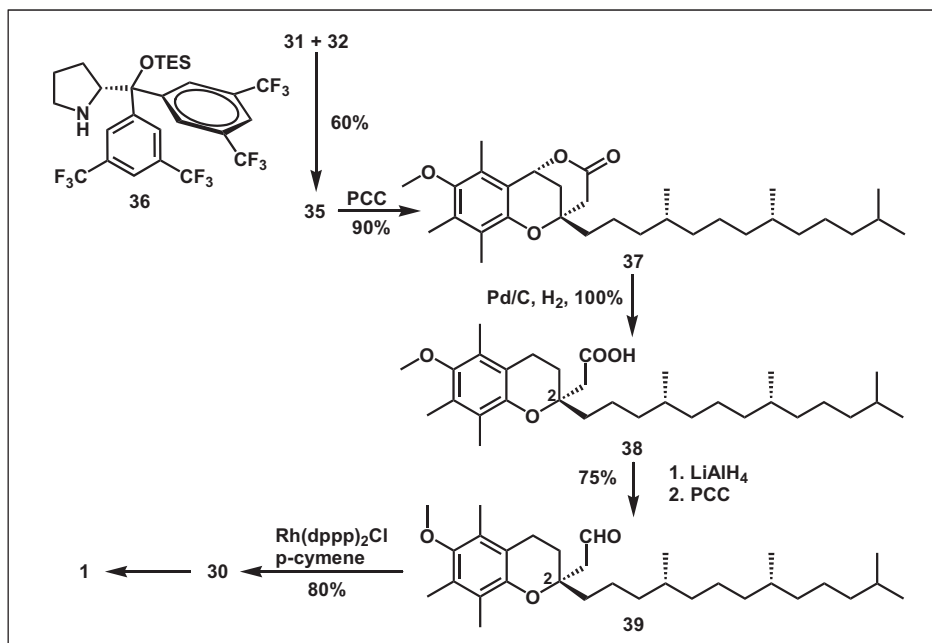
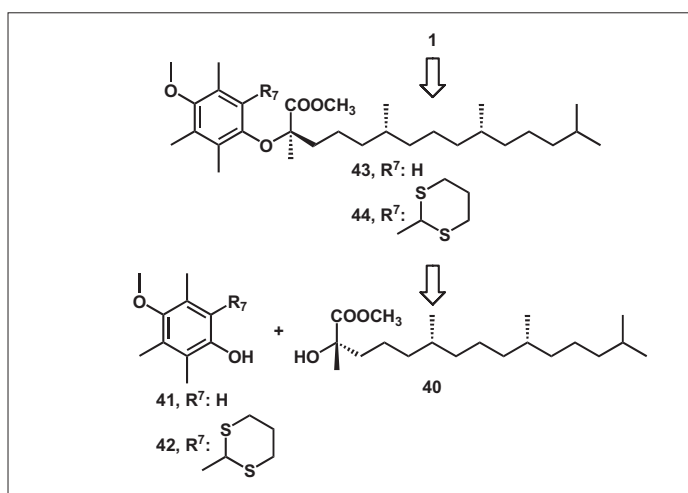
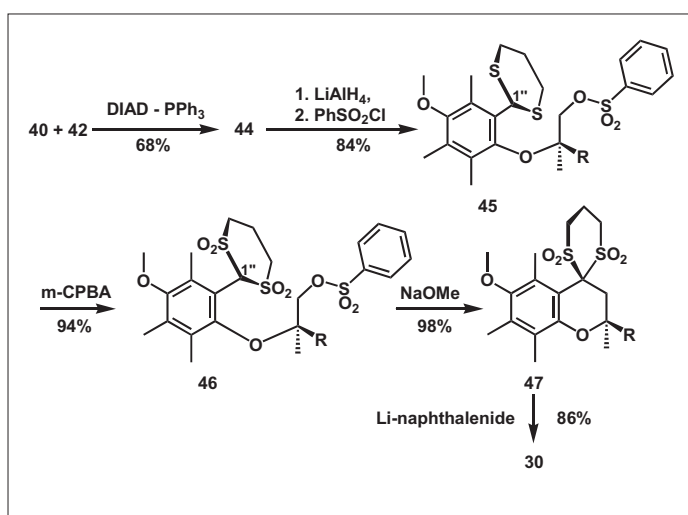
In summary, although the domino reaction requires rather high concentrations (30ml%) of the proline derivative **36** the stereoselectivity and diastereoselectivity of this step are excellent providing one of the shortest procedures to obtain natural α -tocopherol (**1**). This strategy provides a general access to other members of the vitamin E family and further to various natural products containing highly substituted, chiral chromanols^[20] or xanthenes.^[21]

2.3 Coupling of Phenols with the Side Chain Containing the Required Three Chiral Centers

Several earlier syntheses of vitamin E compounds reported the preparation of the chiral chromanol using side chains that contain already all chiral centers.^[6] Our unprecedented approach^[22] employed the chiral key intermediate **40** which was planned to react under Mitsunobu conditions with phenols **41** and **42** generating chiral phenolethers **43** and **44** that could be further elaborated for the preparation of **1** (Scheme 11). The α -hydroxyester **40** was chosen because model reactions revealed that replacement of the ester by CN, $\text{CH}=\text{CH}_2$, CHO and propargyl substituents was unsatisfactory and gave <20% yield of phenol ethers.

Mitsunobu reaction of **40** with **41** or **42** gave phenol ethers **43** and **44** with complete inversion of configuration and 64% and 68% yield, respectively. As the thioke-tal **45** derived from **44** did not cyclize in the presence of $n\text{BuLi}$ ^[23] the corresponding bis-sulfone **46** was prepared^[24] that gave the chromane **47** in 98% yield on treatment with NaOMe. Reductive removal of the dithiane tetroxide moiety was achieved with excess lithium naphthalenide yielding tocopheryl methylether **30** in 86% yield and 94% *de* (Scheme 12).

Alternatively **43** was reduced to aldehyde **48** and subsequent Wittig reaction, hydroboration and oxidation gave aldehyde **49** that cyclized in the presence of TFA to furnish the chromene **50** in excellent yield

Scheme 10. Organocatalytic synthesis of α -tocopherol (1)Scheme 11. Retrosynthesis of **1** using the Mitsunobu reaction between phenols and α -hydroxyester **40**.Scheme 12. Chromanol ring closure using the tetraoxido 1,3 dithiane **46**.

(Scheme 13). Hydrogenation of **50** followed by deprotection gave α -tocopherol (**1**) displaying 94% *de*.

The key step of both pathways to α -tocopherol (**1**) is a carefully controlled Mitsunobu reaction that generates the required phenylether with high *de*. Consecutive ring closure to the chromane/chromene was accomplished by two different procedures without epimerization.

3. Conclusion

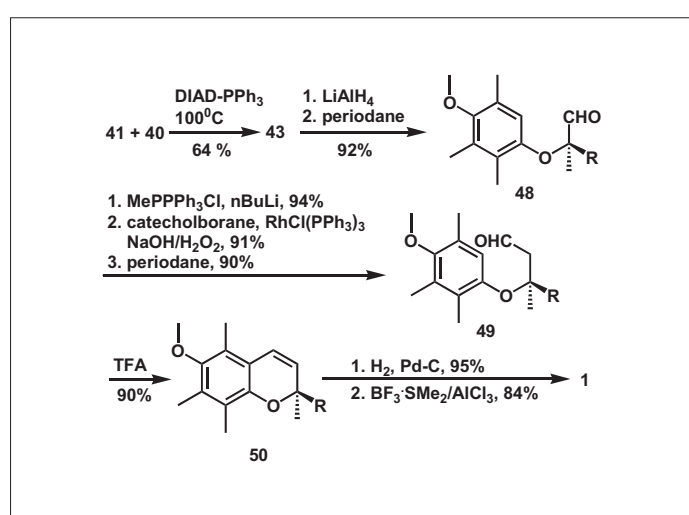
Using a phytylhydroquinone derivative that allows for diastereoselective acid-driven double bond activation we developed an enzyme-like formation of the chromanol unit of α -tocopherol. Subsequently we employed two organocatalytic reactions as key steps towards diastereoisomerically enriched **1**, and further a Mitsunobu reaction was used coupling a suitable phenol with a chiral α -hydroxyester under complete inversion of configuration. Except for the biomimetic cyclization all other approaches gave **1** displaying *de* well above 90%.

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- [1] J.-M. Zingg, *Mol. Asp. Med.* **2007**, 28, 481.
- [2] E. Reiter, Q. Jang, S. Christen, *Mol. Asp. Med.* **2007**, 28, 668.
- [3] G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, 19, 194.
- [4] G.W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, K. U. Ingold, *J. Am. Chem. Soc.* **1985**, 107, 7053.

Scheme 13. Chromanol ring closure *via* electrophilic aromatic substitution.

- [5] R. Meier, T. Tomizaki, C. Schulze-Briese, U. Baumann, A. Stocker, *J. Mol. Biology* **2003**, *331*, 725.
- [6] T. Netscher in 'Vitamins and Hormones', Vol. 76, Ed. G. Litwack, Elsevier, San Diego, **2007**, pp. 155–202.
- [7] A. Stocker, A. Rüttimann, W.-D. Woggon, *Helv. Chim. Acta* **1993**, *76*, 1729.
- [8] A. Stocker, H. Freitz, H. Frick, A. Rüttimann, W.-D. Woggon, *Biorg. Med. Chem.* **1996**, *4*, 1129.
- [9] A. Stocker, T. Netscher, A. Rüttimann, R. K. Müller, H. Schneider, L. J. Todaro, G. Derungs, W.-D. Woggon, *Helv. Chim. Acta* **1994**, *77*, 1721.
- [10] C. Grütter, E. Alonso, A. Chougnet, W.-D. Woggon, *Angew. Chem., Int. Ed.* **2006**, *45*, 1126.
- [11] S. Bell, B. Wüstenberg, S. Kaiser, F. Menges, T. Netscher, A. Pfaltz, *Science* **2006**, *311*, 642.
- [12] J. Chapelat, A. Chougnet, W.-D. Woggon, *Eur. J. Org. Chem.* **2009**, 2069.
- [13] M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377.
- [14] I. Vilotijevic, T. F. Jamison, *Science* **2007**, *317*, 1189.
- [15] J. Baldwin, *J. Chem. Soc. Chem. Commun.* **1976**, *18*, 734.
- [16] S. V. Ley, *Asymmetric Synthesis* **2007**, 201.
- [17] K. Liu, A. Chougnet, W.-D. Woggon, *Angew. Chem., Int. Ed.* **2008**, *47*, 5827.
- [18] M. Kreis, A. Palmelund, L. Bunch, R. Madsen, *Adv. Synth. Catal.* **2006**, *348*, 2148.
- [19] D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron* **1985**, *41*, 3901.
- [20] K. Liu, W.-D. Woggon, *Eur. J. Org. Chem.* **2010**, *6*, 1033.
- [21] N. Volz, M. C. Bröhmer, M. Nieger, S. Bräse, *Synlett* **2009**, *4*, 550.
- [22] U. Hengartner, A. Chougnet, K. Liu, W.-D. Woggon, *Chem. Eur. J.* **2010**, *16*, 1306.
- [23] D. Seebach, E.-M. Wilka, *Synthesis* **1976**, 476.
- [24] H. Ramuz, *Cardiology* **1982**, *69*, 26.