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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 biologically 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.

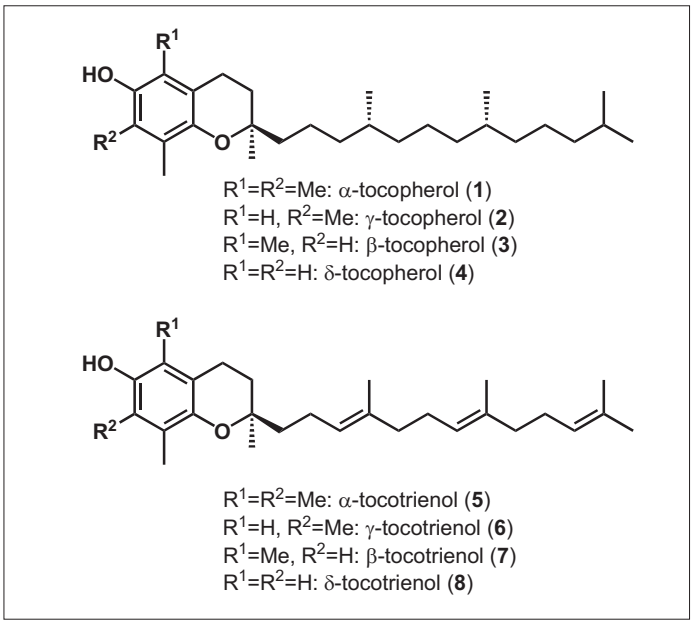
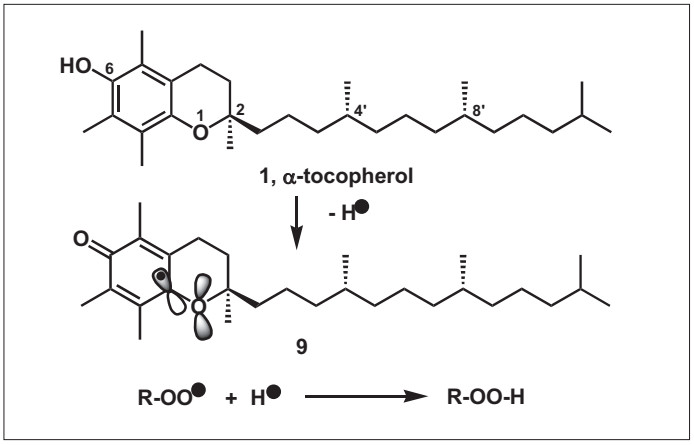


Fig. 1. Structures of vitamin E compounds.



Scheme 1. Antioxidant reactivity of **1**: Formation of tocopheryl radicals such as **9** and trapping of peroxy radicals ROO· 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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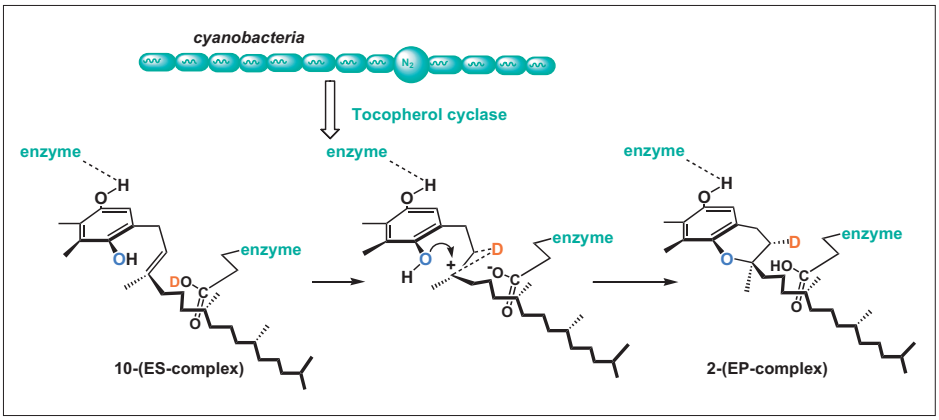
precursors with chiral and unsaturated side chains leading to **2** and **6**, respectively, with the comparable efficiency; and ii) the very hydrophobic 42 kD protein operates by *si* protonation of the double bond and concomitant *re* attack of the phenol (Scheme 2).

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).

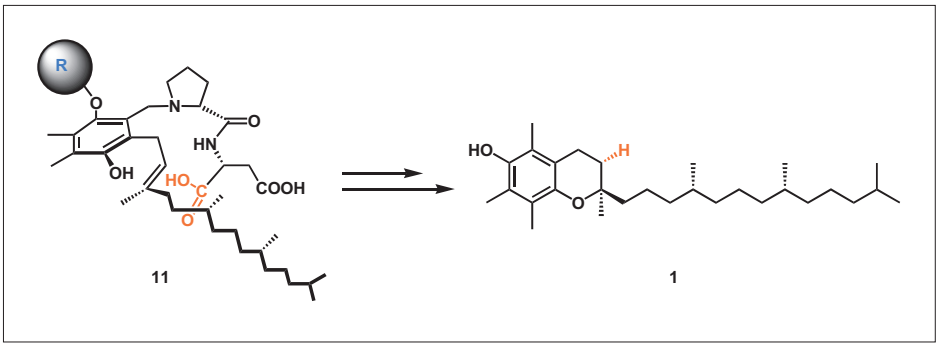
The general strategy to obtain a suitable precursor for cyclization to the chromanol system of vitamin E is outlined in Fig. 2. It was anticipated that cyclization would proceed with the chiral side chain leading directly to **1** as well as with the unsaturated side chain yielding α-tocotrienol (**5**)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

Accordingly, the synthesis of **1** started with the monoprotected hydroquionone **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 acetatel (**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**).

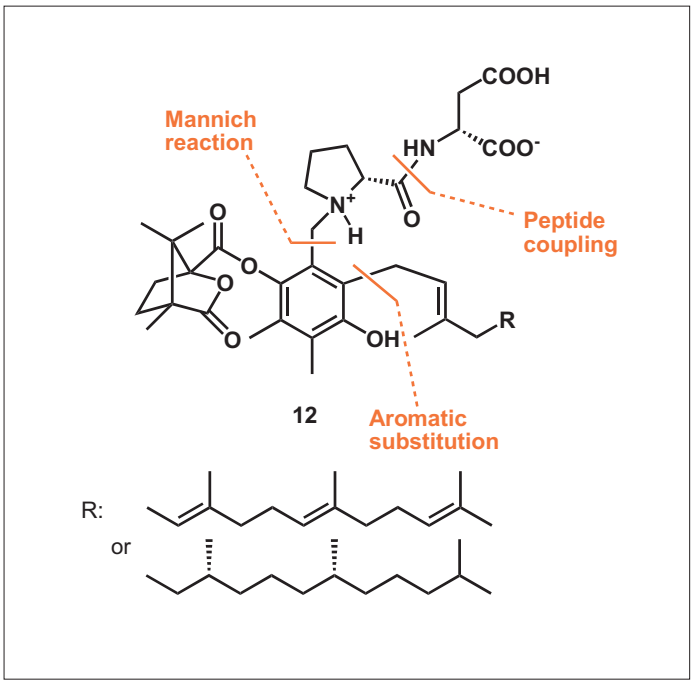


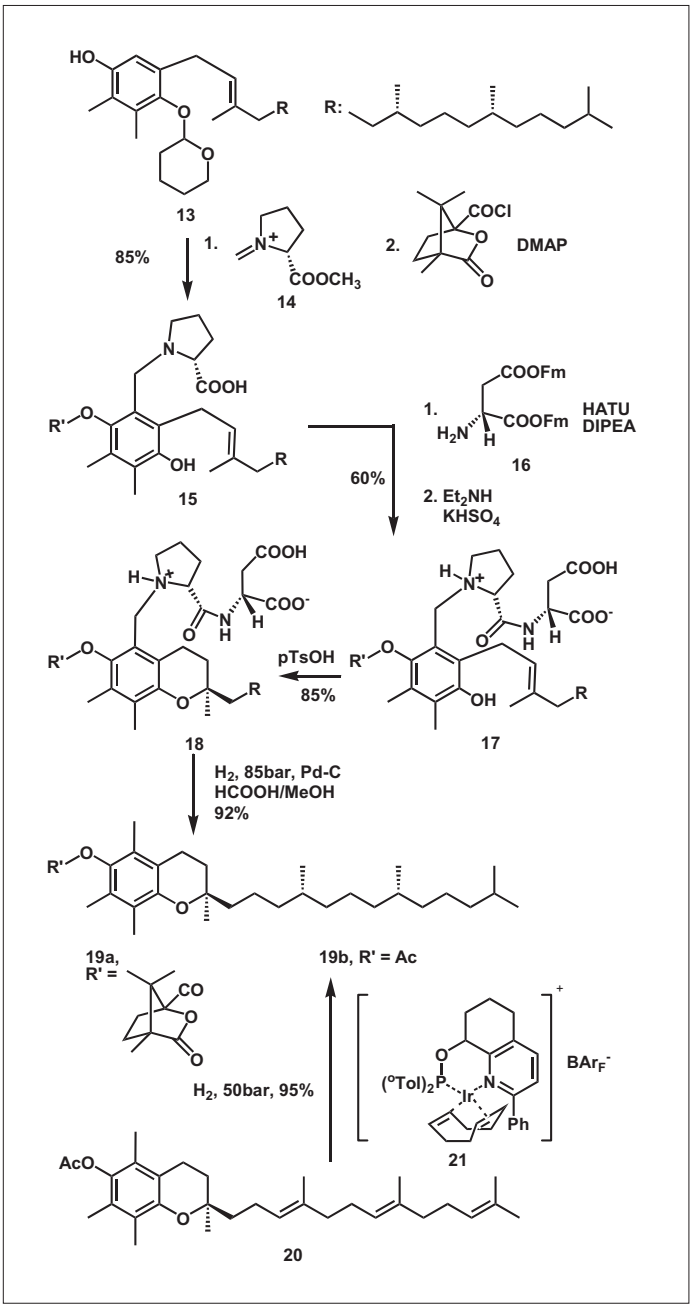
Fig. 2. Retrosynthetic analysis to generate the allylic phenol **12** for cyclization.

2.2 *Organocatalytic Keysteps for the Synthesis of Chromanols*

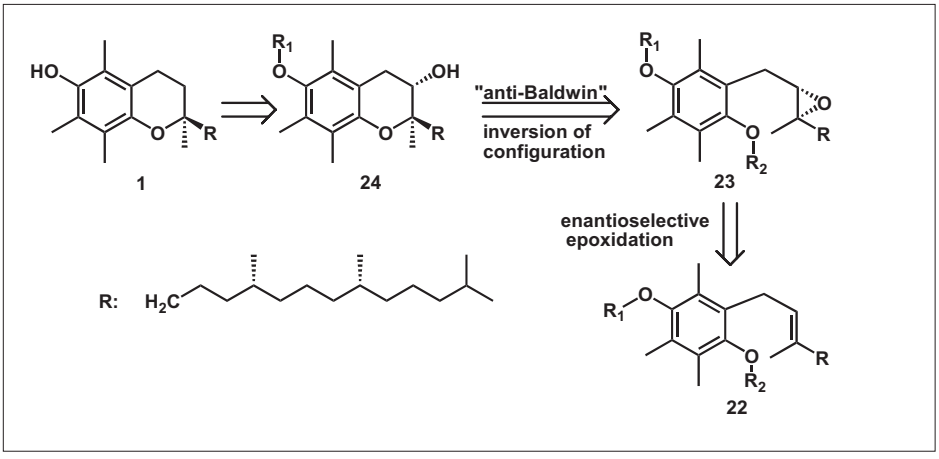
2.2.1 *Organocatalysis Using Chiral Dioxetans*

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

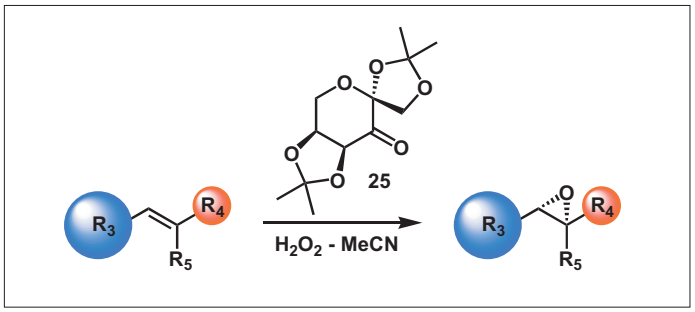
Regarding enantioselective epoxidation we considered the application of organocatalysts developed by Zhao and Shi.[13] This group has reported that fructose-derived compounds such as **25** (+ H_2O_2) cata-



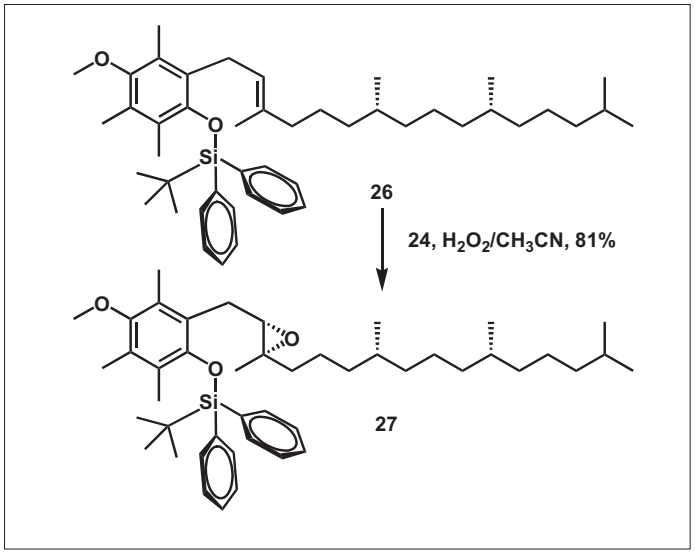
Scheme 4. Biomimetic synthesis of α-tocopheryl- and α-tocotrinenyl esters.



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.

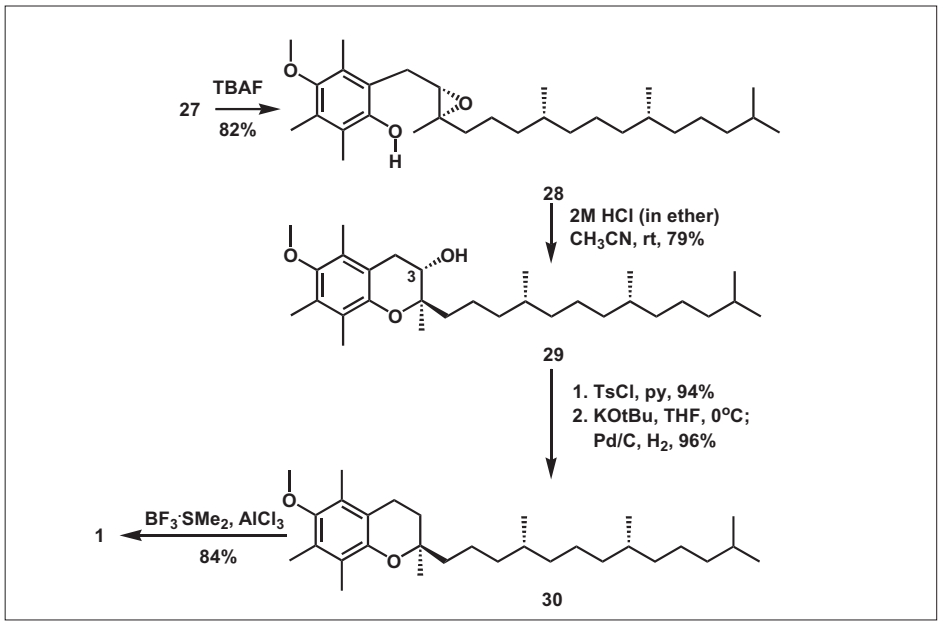


Scheme 7. Diastereoselective 'Shi-epoxidation'.

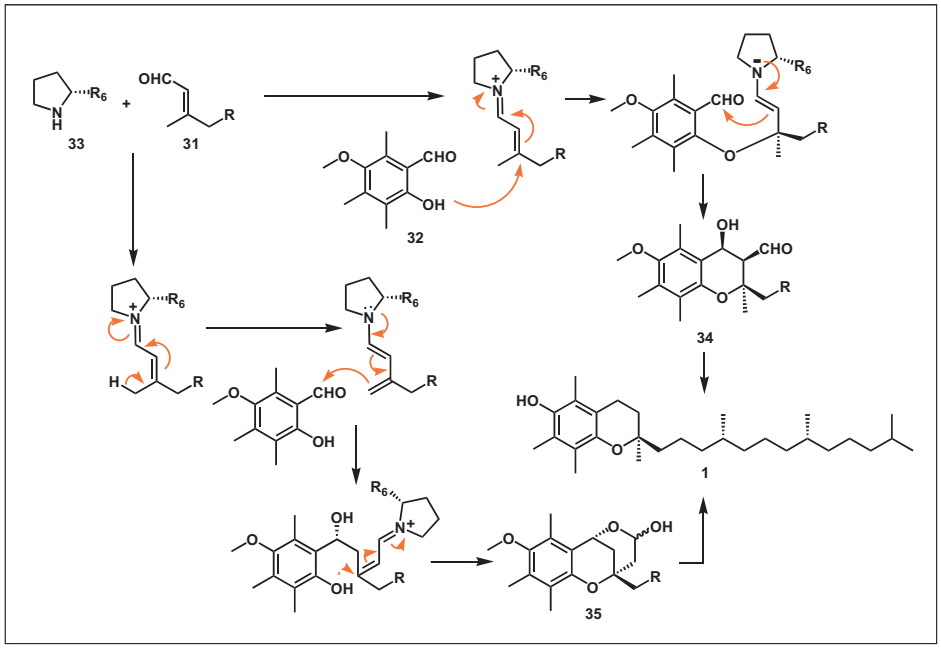
lyze the formation of chiral epoxides provided the olefin contains groups R_3 and R_4 that are very different in size (Scheme 6).

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 $BF_3{\cdot}SMe_2/AlCl_3$ 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 diasteromeric 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 demethylation, 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 $BF_3{\cdot}Me_2S/AlCl_3$; α-tocopherol (**1**) was obtained in 84% yield under retention of configuration at C(2).

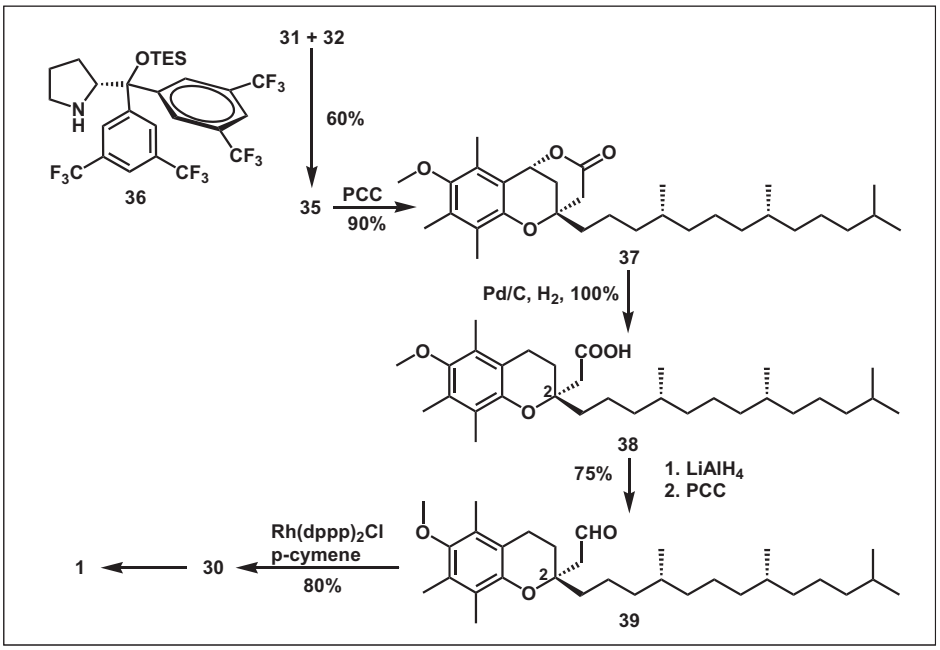
In summary, although the domino reaction requires rather high concentrations (30ml%) of the proline derivative **36** the stereoselectivity and diastereoselectivity of this step are excellent providing one of the shortest procedures to obtain natural α-tocopherol (**1**). This strategy provides a general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

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

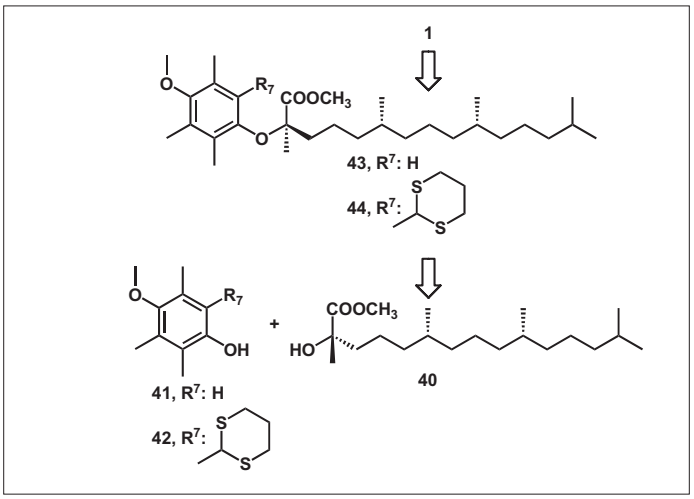
Several earlier syntheses of vitamin E compounds reported the preparation of the chiral chromanol using side chains that contain already all chiral centers.[6] Our unprecedented approach[22] employed the chiral key intermediate **40** which was planned to react under Mitsunobu conditions with phenols **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, $CH{=}CH_2$, 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 thioketal **45** derived from **44** did not cyclize in the presence of nBuLi[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).

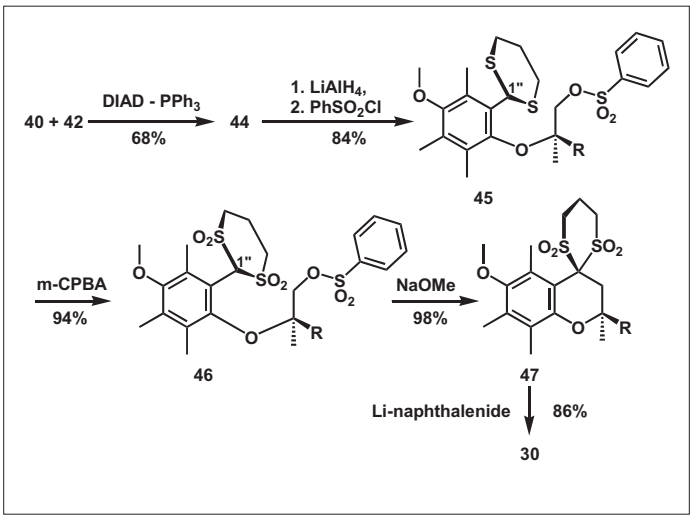
Alternatively **43** was reduced to aldehyde **48** and subsequent Wittig reaction, hydroboration and oxidation gave aldehyde **49** that cyclized in the presence of TFA to furnish the chromene **50** in excellent yield



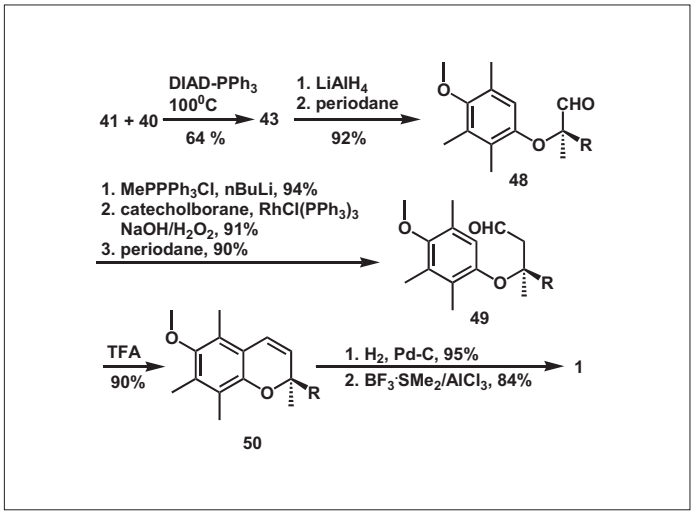
Scheme 10. Organocatalytic synthesis of α-tocopherol (**1**)



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. Chromanol ring closure *via* electrophilic aromatic substitution.

(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 phenolether 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%.

Acknowledgements

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