Natural Products

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A Short Route to α-Tocopherol**

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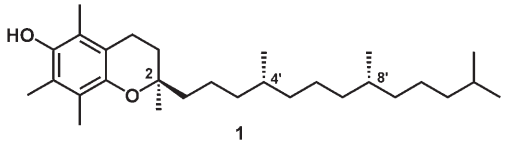
α-Tocopherol (**1**) is the biologically most significant member of the vitamin E family and known to act as a very efficient radical-chain-breaking antioxidant in tissues.[1,2] The isolation



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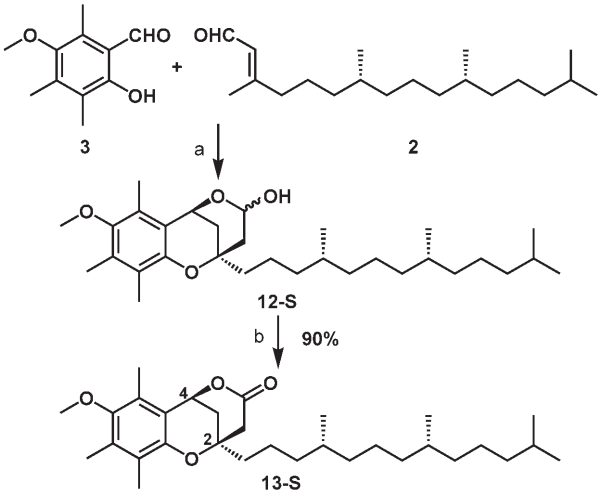
of pure **1** from natural sources, that is, from all photosynthetic organisms, is quite difficult because the compound appears in various amounts along with other vitamin E chromanols. The challenge to preparing enantiomerically enriched **1** derives from the stereogenic centers at C2, C4′, and C8′. In most published reports, the focus was either on the synthesis of chiral chromanols or on the generation of the side chain stereochemistry; there are only a few examples of complete syntheses of **1**.[3,4]

We recently published a biomimetic synthesis of **1**,[5] which was based on the mechanism of chromanol formation[6] as catalyzed by the enzyme tocopherol cyclase from *Cyanobacteria*[7] Herein we report an alternative strategy employing a diastereoselective domino aldol/oxa-Michael reaction[8,9] as the key step by using a diarylprolinol derived catalyst.[10]

Phytol was quantitatively oxidized to phytenal (**2**; Scheme 1),[11] which was then reacted with *ortho*-hydroxy aldehyde **3**[12] by using various proline-derived organocatalysts (**4**–*S*-**11**)[13,10b] (Table 1). Optimal conditions were obtained by using *S*-**11**, to yield hemiacetal **12-S**, which was subsequently oxidized to lactone **13-S** in an overall yield of 52% and with a *de* value of 97%. The absolute configuration at C2 of **13-S** was deduced from the α-tocopherol that was derived from **13-S**, whereas the relative configuration was inferred from an X-ray crystallographic structure of related lactone **14-S**, made from citral by the same reaction sequence (Figure 1).

The formation of lactol **12-S** suggests a reaction sequence such as the one depicted in Scheme 2. The initially produced iminium salt (**15**) leads to dienamine **16**, which reacts with salicylaldehyde **3** to yield the intermediate **17** (aldol reaction). Compound **17** which then cyclizes diastereoselectively to give **12-S** (oxa-Michael addition) and releases the proline derivative. The aldol reaction is the key step that controls the stereoselectivity of the formation of the *syn* arrangement of the six-membered lactol.

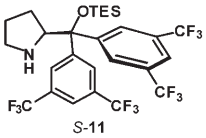
To our delight, benzylic lactone **13-S** was readily hydrogenated quantitatively to afford acid **18-S** (Scheme 3). Only



Scheme 1. Domino aldol/oxa-Michael reaction. Reagents and conditions: a) **4**–*S*-**11**, benzoic acid, toluene; b) PCC, 4 Å M.S., DCM; 90%. PCC = pyridinium chlorochromate, M.S. = molecular sieves; DCM = dichloromethane.

Table 1: Various proline derivatives promoting the reaction of **3** and **2**.

4 R: CH(Ph)$_2$
5 R: C(Ph)$_2$-OTMS
6 R: C(4-CH$_3$C$_6$H$_4$)$_2$-OTMS
7 R: C(4-CF$_3$C$_6$H$_4$)$_2$-OH
8 R: C(4-CF$_3$C$_6$H$_4$)$_2$-OTMS
9 R: C(Ph)$_2$-F
10 R: C(4-CF$_3$C$_6$H$_4$)$_2$-F



S-11

Entry	Amine[a]	Solvent	*t* [h]	Yield [%][b]	*de* [%][c]
1	**4**	Et_2O	67	21	27
2	**5**	*n*-hexane	69	33	55
3	**6**	toluene	120	18	n.d.
4	**7**	toluene	96	10	n.d.
5	**8**	CH_2Cl_2	110	27	44
6	**8**	toluene	68	41	87
7	**9**	toluene	72	31	75
8	**10**	toluene	72	13	90
9	*S*-**11**	toluene	72	58	97

[a] 30 mol%, all reactions were performed at RT. [b] Yields of isolated **12-S**. [c] Diastereomeric excess (*de*) was determined for corresponding lactone **13-S** by chiral HPLC analysis. TES = triethylsilyl; n.d. = not determined.

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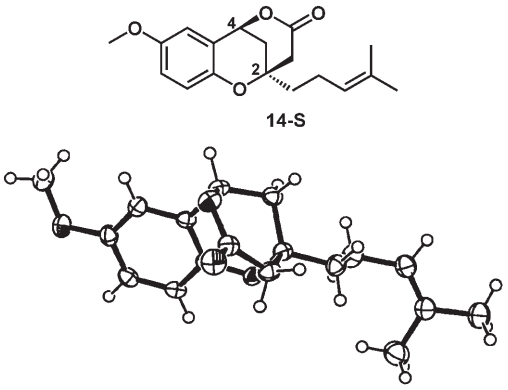
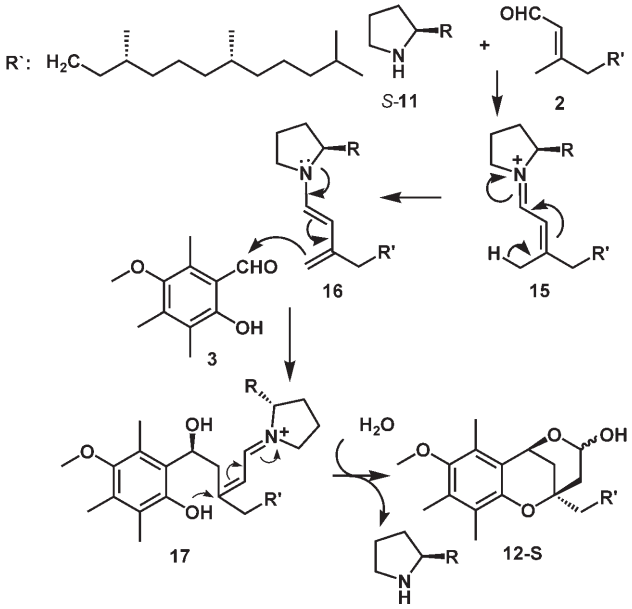
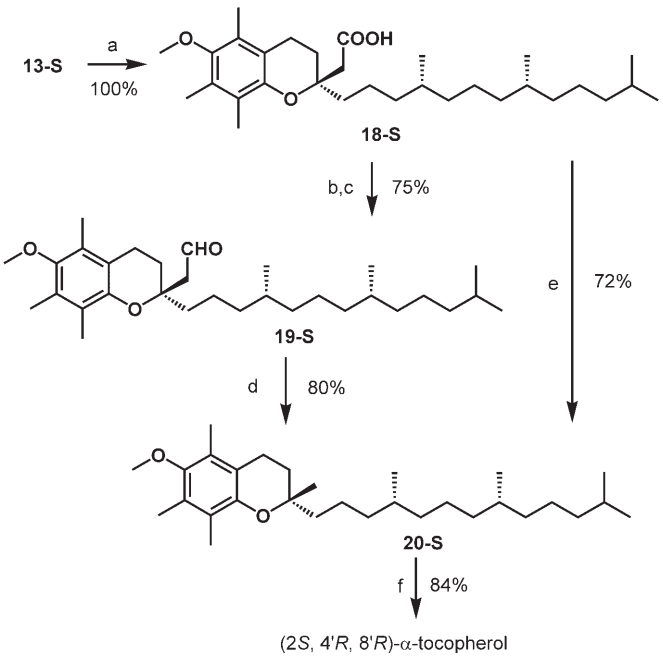


Figure 1. X-ray crystallographic structure of **14-S** reveals the *syn* arrangement of lactone **14-S**, an analogue of **13-S**.



Scheme 2. Proposed mechanism for domino aldol/oxa-Michael reaction leading to **12-S**.

two additional steps, that is, the removal of one carbon atom and a demethylation, are required to convert key intermediate **18-S** into α-tocopherol. However, conditions had to be carefully tuned to prevent racemization at C2 because of thermal or acid-catalyzed ring opening/ring closure of the chromane system. Finally, two procedures were found to excise a carbon atom to arrive at the methyl group at C2. Reduction of acid **18-S** and subsequent oxidation gave aldehyde **19-S** in 75% yield. Subsequent Rh-catalyzed decarbonylation[14] furnished α-tocopherol ether **20-S** in 80% yield and 93% *de*. The same compound was obtained in 72% yield and 94% *de* by using a Barton decarboxylation procedure.[15] After several attempts with various Lewis acids, cleavage of the ether was accomplished by treating **20-S** with $BF_3{\cdot}Me_2S/AlCl_3$; α-tocopherol was obtained in 84% yield with retention of the configuration at C2. Chiral HPLC analysis revealed that this α-tocopherol sample has an

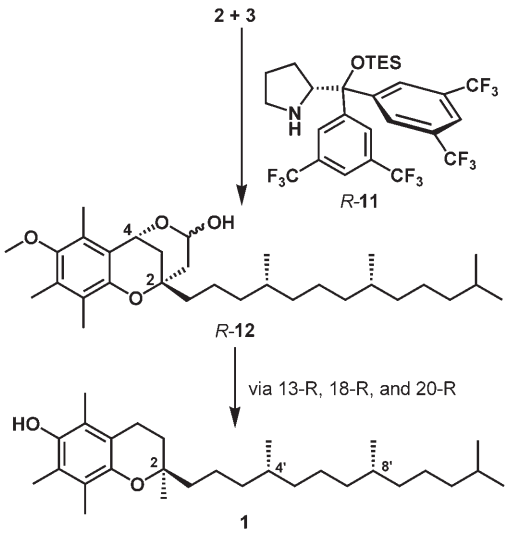


Scheme 3. Synthesis of 2S configured α-tocopherol. Reagents and conditions: a) H_2 10% Pd/C, methanol, DCM; 100%; b) $LiAlH_4$, THF; c) PCC, 4 Å M.S., DCM; 75% in two steps; d) $[Rh(dppp)_2Cl]$, *p*-cymene, N_2 stream, 80%; e) $(COCl)_2$, benzene/2-mercaptopyridine-1-oxide sodium salt, *t*BuSH, toluene, reflux; 72%; f) $BF_3{\cdot}Me_2S$, $AlCl_3$, MeCN, DCM; 84%. dppp = 1,3-bis(diphenylphosphino)propane.

S configuration at C2, which is the configuration for unnatural α-tocopherol (see the Supporting Information).

Consequently proline catalyst enantiomer *R*-**11** was employed for the domino reaction and the resulting lactol was converted, as described above, into α-tocopherol (**1**) in an overall yield of 29% and with a 93% diastereomeric excess (Scheme 4).

In summary, although the domino reaction requires rather high concentrations of proline derivatives *S*-**11** or *R*-**11**, the



Scheme 4. Synthesis of (all-*R*)-α-tocopherol (**1**).

stereoselectivity and enantioselectivity of this step are excellent in providing one of the shortest procedures to obtain (all-*R*)-α-tocopherol (**1**). To the best of our knowledge, this is the first application of an organocatalyst to the construction of chromanols, having a tetrasubstituted chiral carbon center, in high diastereoselectivity. This strategy provides general access to other members of the vitamin E family, as well as to other natural products containing highly substituted, chiral chromanols.

Experimental Section

Detailed descriptions of the syntheses and spectroscopic details of all compounds are given in the Supporting Information. CCDC-691286 (**14-S**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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