

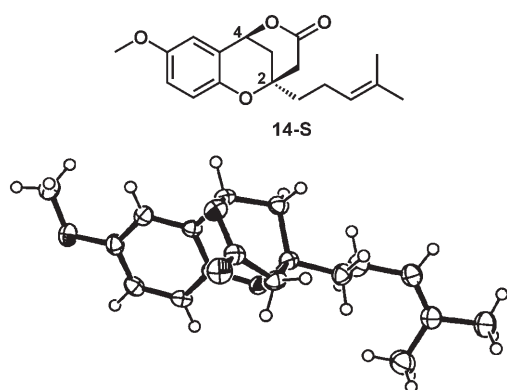
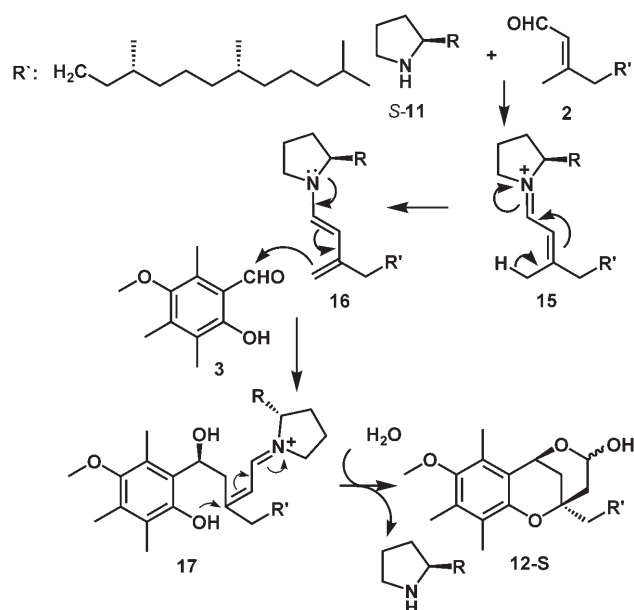
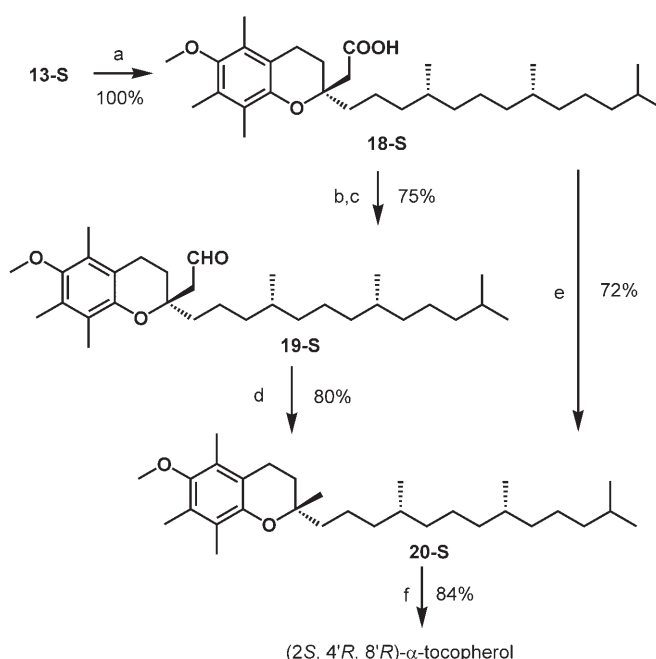


Figure 1. X-ray crystallographic structure of **14-S** reveals the *syn* arrangement of lactone **14-S**, an analogue of **13-S**.



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 $\text{BF}_3 \cdot \text{Me}_2\text{S}/\text{AlCl}_3$; 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

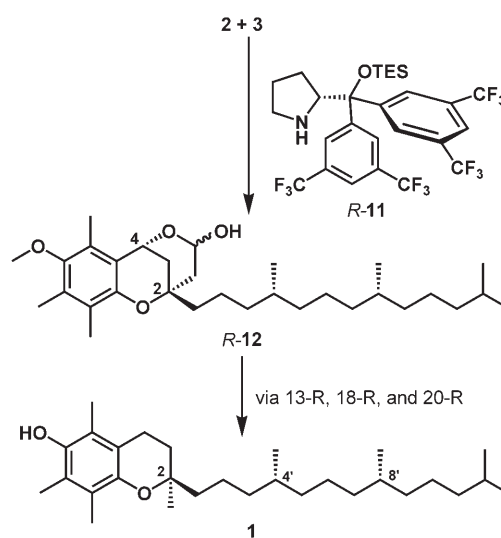


Scheme 3. Synthesis of 2S configured α -tocopherol. Reagents and conditions: a) H_2 10% Pd/C, methanol, DCM; 100%; b) LiAlH_4 , THF; c) PCC, 4 Å M.S., DCM; 75% in two steps; d) $[\text{Rh}(\text{dppp})_2\text{Cl}]$, *p*-cymene, N_2 stream, 80%; e) $(\text{COCl})_2$, benzene/2-mercaptopyridine-1-oxide sodium salt, *t*BuSH, toluene, reflux; 72%; f) $\text{BF}_3 \cdot \text{Me}_2\text{S}$, 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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