Total Synthesis of (2*R*, 4´*R*, 8´*R*)-α-Tocopherol

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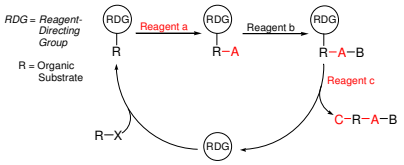
Introduction

The importance of Vitamin E (α-Tocopherol) for human health is well known. It is a potent antioxidant and radical scavenger in chemical and biological systems and has been receiving increasing attention with regard to clinical and nutritional applications. Exhaustive investigations of the total synthesis of the naturally occurring form (2*R*, 4´*R*, 8´*R*)-α-Tocopherol (**1**) has been made in the 60´s and the 70´s.[1]

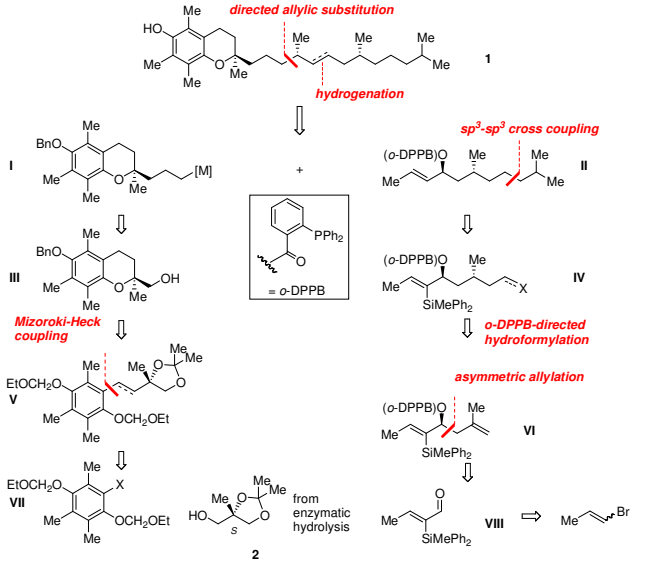
Herein, we wish to report the enantioselective total synthesis of (2*R*, 4´*R*, 8´*R*)-α-Tocopherol in which the side chain is constructed in an entirely novel manner relying on the concept of a *RDG*-controlled organic synthesis.



Basic idea of this strategy is the multiple use of a reagent-directing group (*RDG*) in order to control reaction selectivity. Removal of the *RDG* should be achieved in a final *RDG*-controlled fragment coupling step.

Synthesis Plan

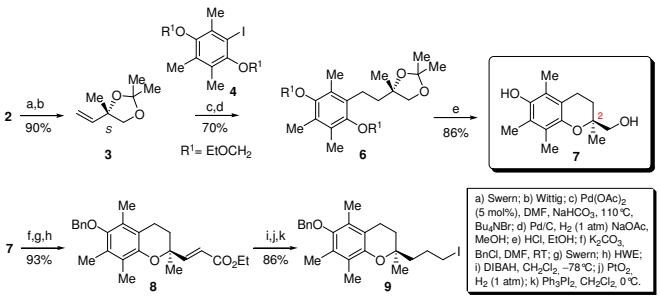
Our strategy is based on the copper-mediated *ortho*-diphenylphosphanylbenzoyl (*o*-DPPB) group-directed allylic substitution and the rhodium-catalyzed *o*-DPPB- directed hydroformylation which have been developed in our laboratories recently.[2]



A catalytic asymmetric allylation was envisioned as the key step for the entrance into the right configuration of the stereogenic centers in the side chain.

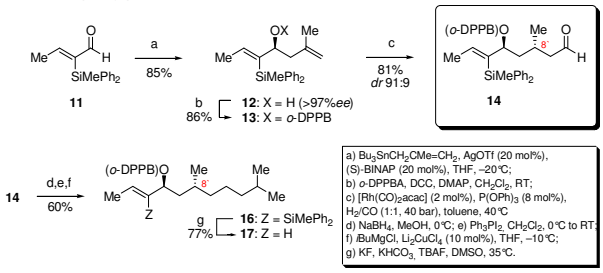
Synthesis of the chroman system

Construction of the chroman system began with alcohol **2** which was obtained from an efficient enzymatic ester hydrolysis.[3] Key steps were the Heck coupling[4] of alkene **3** and the one-pot Brønsted acid catalyzed deprotection and cyclization which gave the fully functionalized chroman system **7**[5,6] in excellent yield with complete retention of configuration[7,8] (*ee* 99.5%).



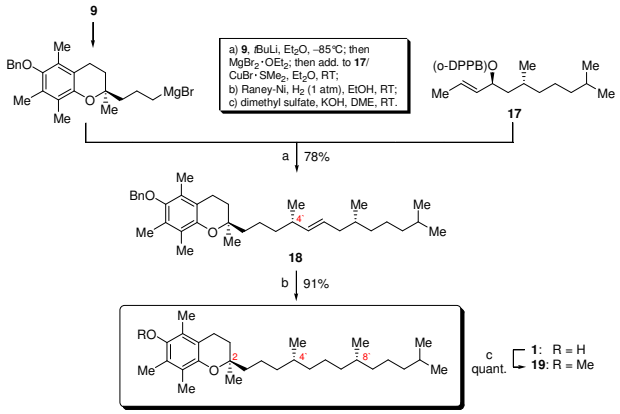
Synthesis of the isoprenoid side chain

Synthesis of the C16-isoprenoid side chain of Tocopherol began with a three step synthesis[9] to aldehyde **11**.[10] Catalytic asymmetric allylation gave the homomethallylic alcohol **12** in gram scale with greater 97% *ee*. Next, the reagent-directing *o*-DPPB group was installed to furnish the substrate for an *o*-DPPB-directed rhodium catalyzed hydroformylation.[11] Thus, the corresponding *anti*-aldehyde **14** was obtained in 81% yield and a diastereoselectivity of 91:9. Reduction and transformation of the aldehyde furnished the corresponding iodide, which allowed a copper-catalyzed sp^3-sp^3 cross coupling reaction to vinylsilane **16**, which was protodesilylated to give fragment coupling precursor **17**.



Final coupling step

As the final fragment coupling step *o*-DPPB-directed allylic substitution was chosen. We recently demonstrated that this reaction proceeds with high levels of chemo-, regio- and diastereoselectivity, concomitant with a perfect 1,3-chirality transfer. For synthesis completion benzylether deprotection and alkene reduction were accomplished in one pot with Raney-Ni under an atmosphere of hydrogen to give (*R*,*R*,*R*)-α-Tocopherol[12] in 13 steps (longest linear sequence) and 30% overall yield.[13]



Conclusion

A new strategy for making efficient use of substrate control employing the concept of an *RDG*-controlled organic synthesis has been realized. The reagent-directing group (*o*-DPPB) served to control the stereoselectivity in the course of a rhodium-catalyzed hydroformylation reaction and the same *o*-DPPB group acted as a reagent-directing leaving group in the course of a directed copper-mediated allylic substitution, which simultaneously served as the fragment coupling step and lead to the removal of the *o*-DPPB group, which can be recovered in the work-up process. To the best of our knowledge this is also the first application of a copper-mediated allylic substitution as a fragment coupling reaction in the course of a total synthesis, and clearly demonstrates the synthetic potential of *o*-DPPB-directed allylic substitution in total synthesis.

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