Total Synthesis

DOI: 10.1002/ange.200703268

Reagent Directing Group Controlled Organic Synthesis: Total Synthesis of (*R*,*R*,*R*)-α-Tocopherol**

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Selectivity control during the course of a total synthesis can be achieved either by the reagents employed (reagent control) or, generally less frequently used, by the substrate (substrate control). However, the latter approach could be particularly efficient if attractive substrate–reagent interactions are involved which allow for the optimal transfer of a substrate's structural information into the associated selectivity-determining transition state of a subsequent transformation.[1] One way to enforce such attractive substrate–reagent interactions is to employ substrate-bound reagent-directing groups (RDGs, Figure 1).[2] In an ideal scenario, such an RDG

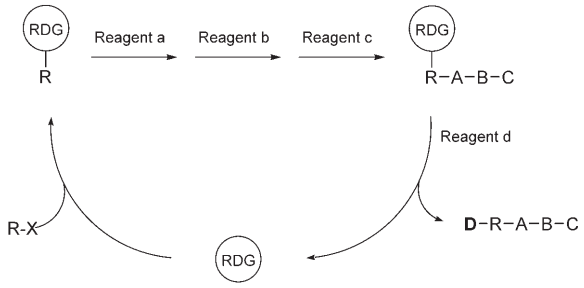

Figure 1. Concept of reagent directing group (RDG) controlled organic synthesis.

would not only control the selectivity of a single transformation but also a sequence of reactions that introduce structural elaborations (with reagents a,b,c) until it is finally removed from the product. Ideally, the removal step (reagent d) would be incorporated during the course of a further skeleton-expanding operation, which at best would be a fragment-coupling step at a late stage of the synthesis. We report herein on the first realization of the concept of an RDG-controlled organic synthesis by an enantioselective total synthesis of (*R*,*R*,*R*)-α-tocopherol (**1**).

(*R*,*R*,*R*)-α-Tocopherol (**1**) is the most prominent and biologically most active naturally occurring member of the compounds covered by the term vitamin E, which is an essential food ingredient and the most important fat-soluble antioxidant.[3] As a consequence, tocopherol (**1**) has been the target of many synthetic endeavors which have been, however, directed almost exclusively at the stereoselective preparation of either chroman or isoprenoid side-chain building blocks, which then had to be connected in a subsequent step.[4] In contrast, strategies involving, for example, C–C or C–O coupling reactions with concomitant creation of a stereogenic center are rare.[5,6]

Our synthetic plan is outlined in Scheme 1. As a final fragment-coupling step we envisioned using our recently developed *o*-DPPB-directed copper-mediated allylic *syn*-substitution reaction[7] between the tocopherol nucleus **I** functionalized as an organometallic nucleophile and the allylic electrophile **II**. The latter could stem from the aldehyde **IV**, which could be chain-elongated (after reduction and activation) by way of an sp^3–sp^3 cross-coupling reaction. Aldehyde **IV** could be the product of an *o*-DPPB-directed stereoselective hydroformylation of the homomethallylic precursor **VI**.[8] A temporary protecting group Σ for the allylic alkene function might need to be incorporated to shield the double bond from an undesired hydroformylation reaction. A catalytic asymmetric allylation could deliver the alcohol precursor of **VI**.

The heterocyclic organometallic nucleophile **I** could be envisaged to stem from alcohol building block **III**, which itself could be the product of a Brønsted acid catalyzed cyclization of ketal-protected diol **V**. A Heck-type coupling between the aromatic system **VII** and a C_1-chain-elongated terminal alkene derived from the known alcohol **2** could be used for installation of the isoprenoid side chain into the cyclized precursor.[9]

Construction of the chroman system began with alcohol **2**, which was obtained from an efficient enzymatic ester hydrolysis.[9] Oxidation and Wittig olefination furnished alkene **3** (Scheme 2). A subsequent Mizoroki–Heck coupling reaction[10] with aryl iodide **4** proceeded smoothly under the conditions developed by Jeffrey[11] to furnish the hexasubstituted arene system **5** in 75% yield. After hydrogenation of the alkene to give **6**, a one-pot Brønsted acid catalyzed deprotection and cyclization gave the fully functionalized chroman system **7**[12,13] in excellent yield and with complete retention of configuration[14,15] (99.5% *ee*). After protection of the phenolic hydroxy group as a benzyl ether, the required two-

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[**] This work was supported by the Fonds der Chemischen Industrie, the International Research Training group "Catalysts and Catalytic Reactions for Organic Synthesis" (GRK 1038). We thank Rhodia for the generous gifts of chemicals.

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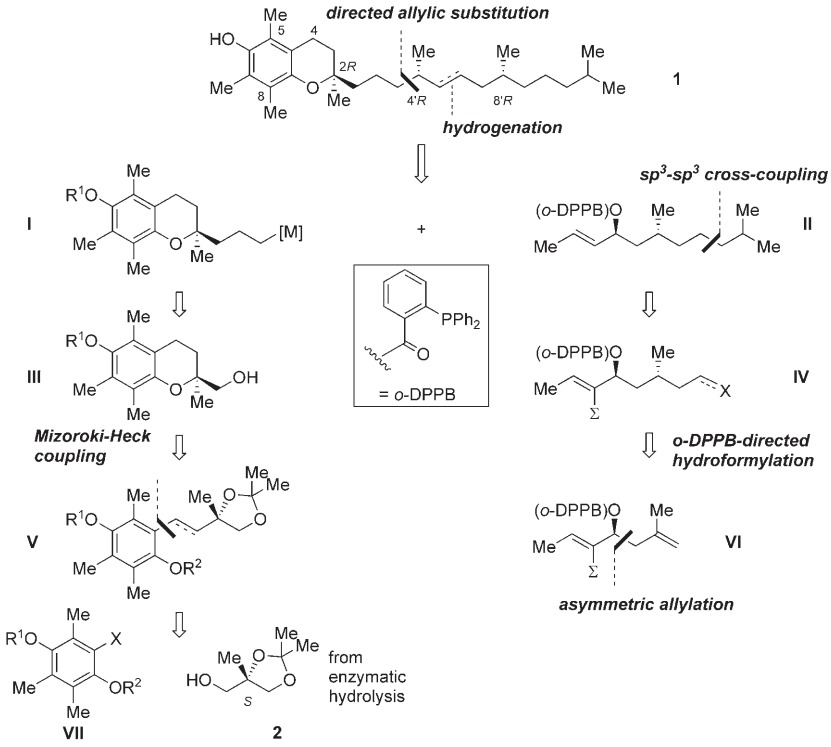
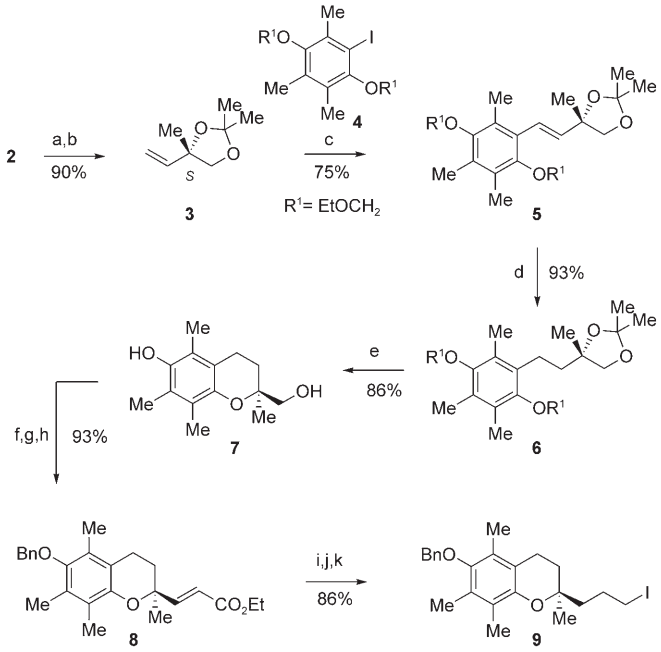


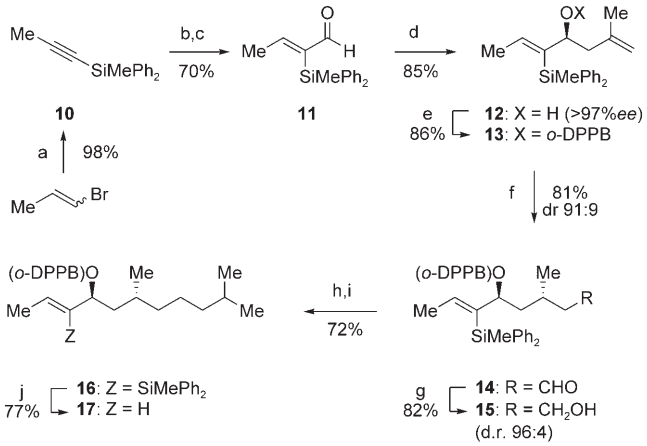
Scheme 1. Synthesis plan. *o*-DPPB = *ortho*-diphenylphosphanyl benzoate).



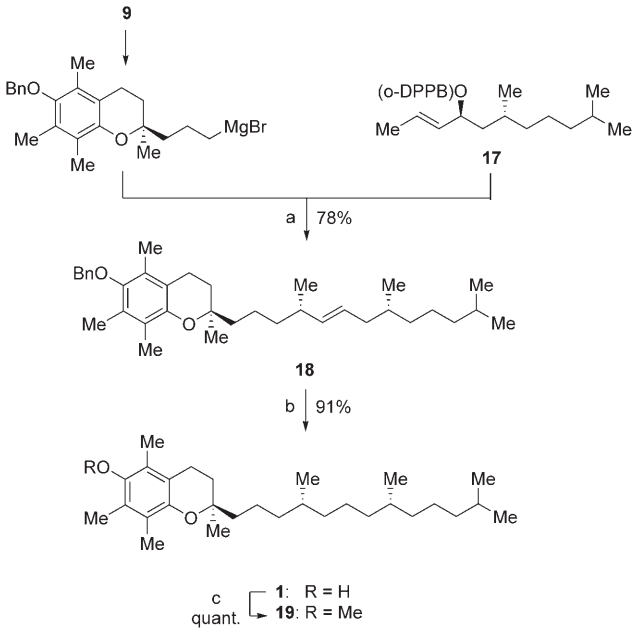
Scheme 2. Synthesis of the chroman system. Reagents and conditions: a) Swern; b) Wittig; c) $Pd(OAc)_2$ (5 mol%), DMF, $NaHCO_3$, 110°C, Bu_4NBr; 75%; d) Pd/C, H_2 (1 atm), NaOAc, MeOH; 93%; e) HCl, EtOH; 86%; f) K_2CO_3, BnCl, DMF, RT; 98%; g) $(COCl)_2$, DMSO, CH_2Cl_2 −50°C, then NEt_3; 98%; h) $(EtO)_2P(O)CH_2CO_2Et$, *n*BuLi, DME, 0°C to RT; 97%; i) DIBAL-H, CH_2Cl_2, −78°C; 98%; j) H_2 (1 atm), PtO_2 (8 mol%), TBME, RT; 95%; k) Ph_3PI_2, CH_2Cl_2, 0°C to RT; 92%. Bn = benzyl, DME = 1,2-dimethoxyethane, DIBAL-H = diisobutylaluminum hydride, TBME = *tert*-butyl methyl ether.

carbon-atom chain elongation was achieved by employing a sequence consisting of alcohol oxidation (Swern) followed by a Horner–Wadsworth–Emmons olefination. A two-step protocol was chosen to effect a chemoselective reduction of the α,β-unsaturated ester to the fully saturated alcohol. Thus, in a first step the ethyl ester was reduced with DIBAL-H to give the corresponding allylic alcohol, which could be hydrogenated cleanly under an atmosphere of hydrogen in the presence of Adam's catalyst. A redox condensation[16] with preformed iodotriphenylphosphonium iodide under the conditions developed by Mukaiyama led to iodide **9**, the precursor for the final fragment-coupling step.

To implement our RDG-controlled synthesis strategy for construction of the isoprenoid side chain, a position-selective hydroformylation of a homomethallylic alkene function in the presence of an allylic alkenic function was needed. However, test experiments revealed that for the parent diene system **VI** ($\Sigma = H$) the required position selectivity could not be achieved, as both alkene functions reacted with similar rates. To solve this problem we decided to install a temporary silicon substituent at the allylic alkene function. It is well-known that hydroformylation of trisubstituted alkenes proceeds in general significantly slower than hydroformylation of disubstituted alkenes.[17] A diphenylmethylsilyl substituent was eventually found to serve this purpose. Thus, synthesis of the C_{16} isoprenoid side chain of tocopherol began by trapping lithiopropyne (generated from 1-bromopropene with 2 equiv *n*BuLi)[18] with chlorodiphenylmethylsilane to give alkyne **10** (Scheme 3). Regioselective hydroalumination with DIBAL-H followed by activation as the corresponding ate complex through reaction with methyllithium allowed for a C_1 chain elongation with paraformaldehyde. Oxidation with Dess–Martin reagent furnished aldehyde **11**.[19] To install the first stereogenic center in an efficient manner, we decided to explore the asymmetric catalytic methallylation of aldehyde **11**. Unfortunately, all attempts to achieve this transformation using the protocol developed by Keck et al. failed,[20] presumably as a consequence of significant steric hinderance. Finally, a silver/binap catalyst developed by Yamamoto turned out to be effective.[21] Under optimized conditions, the homomethallylic alcohol **12** was obtained on a gram scale in 85% yield and with greater than 97% *ee*. Next, the reagent-directing *o*-DPPB group was installed by employing a standard Steglich protocol[22] to furnish the substrate for an *o*-DPPB-directed rhodium-catalyzed hydroformylation.[23] Thus, at a synthesis gas pressure of 40 bar and 40°C, the corresponding *anti*-aldehyde **14** was obtained in 81% yield and a diastereoselectivity of 91:9. Reduction of the aldehyde function with sodium borohydride led to alcohol **15**, and allowed the minor *syn* diastereomer to be separated. Transformation of the primary



Scheme 3. Synthesis of **17**. Reagents and conditions: a) *n*BuLi, THF, −78 °C, then $Ph_2MeSiCl$, −78 °C to RT; 98 %; b) DIBAL-H, Et_2O, 0 °C to RT; then MeLi, −5 °C to RT; then $(CH_2O)_n$; 68 %; c) Dess–Martin periodinane, CH_2Cl_2; 99 %; d) $Bu_3SnCH_2CMe{=}CH_2$; AgOTf (20 mol %), (*S*)-binap (20 mol %), THF, −20 °C; 85 %; e) *o*-DPPBA, DCC, DMAP, CH_2Cl_2, RT; 86 %; f) $[Rh(CO)_2(acac)]$ (2 mol %), $P(OPh)_3$ (8 mol %), H_2/CO (1:1, 40 bar), toluene, 40 °C; 81 %; g) $NaBH_4$, MeOH, 0 °C; 82 %; h) Ph_3PI_2, CH_2Cl_2, 0 °C to RT; i) *i*BuMgCl, Li_2CuCl_4 (10 mol %), THF, −10 °C; 72 % over two steps; j) KF, $KHCO_3$, TBAF, DMSO, 35 °C; 77 %. Tf = trifluoromethanesulfonyl, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, o-DPPBA = *ortho*-diphenylphosphanylbenzoic acid, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, acac = acetylacetonate, TBAF = tetra-*n*-butylammonium fluoride.



Scheme 4. Fragment assembly and completion of the synthesis. Reagents and conditions: a) **9**, *t*BuLi, Et_2O, −85 °C; then $MgBr_2{\cdot}Et_2O$; then addition to **17**/$CuBr{\cdot}SMe_2$, Et_2O, RT; 78 %; b) Raney-Ni, H_2 (1 atm), EtOH, RT; 91 %; c) dimethyl sulfate, KOH, DME, RT; quant.

alcohol function in **15** into the corresponding iodide allowed the remaining isobutyl side chain to be installed through a copper-catalyzed sp^3–sp^3 cross-coupling reaction with isobutylmagnesium chloride.[24] Desilylation of the vinylsilane to generate the fragment-coupling precursor **16** was achieved upon treatment with potassium fluoride and TBAF in the presence of potassium bicarbonate in DMSO at 35 °C.

An *o*-DPPB-directed allylic substitution was chosen as the final fragment-coupling step. We recently demonstrated that this reaction proceeds with high levels of chemo-, regio-, and diastereoselectivity, concomitant with a 1,3-chirality transfer.[7] Furthermore, stoichiometric amounts of organometallic reagent are sufficient to achieve complete conversions, which render this reaction suitable for the coupling of valuable metal–organic building blocks with allylic *o*-DPPB esters. Thus, the Grignard reagent (*t*BuLi, $MgBr_2{\cdot}OEt_2$) of chromanyl iodide **9** was generated at −85 °C in diethyl ether. Reaction with the allylic electrophile **17** at room temperature in the presence of 0.5 equivalents of copper(I) bromide dimethylsulfide initiated a clean and highly selective directed allylic *syn* substitution to give the coupling product **18** in 78 % yield (Scheme 4). For completion of the synthesis, cleavage of the benzyl ether and reduction of the alkene were accomplished in one pot with Raney-Ni under an atmosphere of hydrogen (in EtOH at RT, 91 %) to give (*R*,*R*,*R*)-α-tocopherol in 13 steps (longest linear sequence) and 30 % overall yield. A combination of HPLC and GC analysis of the corresponding methyl ether **19** showed the synthetic material to be identical to the natural material.[25]

In conclusion, a new strategy that makes efficient use of substrate control by employing the concept of an RDG-controlled synthesis has been realized in the context of an enantioselective total synthesis of (*R*,*R*,*R*)-α-tocopherol. Thus, the reagent-directing group (*o*-DPPB) served to control the stereoselectivity during the course of a rhodium-catalyzed hydroformylation reaction for the construction of the C_{16} isoprenoid side chain. The same *o*-DPPB group subsequently acted as a reagent-directing leaving group during the course of a directed copper-mediated allylic substitution, which simultaneously served as the fragment-coupling step and led to the removal of the *o*-DPPB group, which may be recovered during 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 a total synthesis, and clearly demonstrates the synthetic potential of *o*-DPPB-directed allylic substitution for total synthesis.

Received: July 21, 2007
Published online: October 12, 2007

Keywords: enantioselectivity · homogeneous catalysis · hydroformylation · isoprenoids · vitamin E

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[25] For the separation of the four diastereomeric pairs of enantiomers by GC, see W. Walther, T. Netscher, *Chirality* **1996**, *8*, 397 – 401; the four 2*R* stereoisomers of **19** were quantified by HPLC on a Chiracel OD column. For details see the Supporting Information.

