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Vitamin E Synthesis

Total Synthesis of (*R*,*R*,*R*)-α-Tocopherol Through Asymmetric Cu-Catalyzed 1,4-Addition

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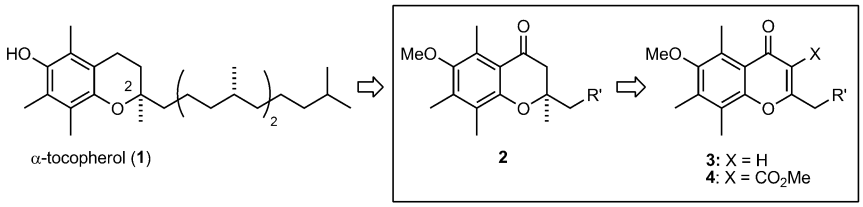
Abstract: By introducing a disposable activating substituent at C-3, the asymmetric 1,4-addition to a notoriously unreactive 2-substituted chromenone was achieved with high levels of (2*R*)-stereoselectivity in the presence of a chiral Cu^{I}-phosphoramidite complex as a catalyst. This paved the way for an efficient and conceptually novel synthesis of (*R*,*R*,*R*)-α-tocopherol from readily available starting materials.

Due to its physiological importance and powerful antioxidant properties α-tocopherol (**1**), which is the most prominent member of the vitamin E family of compounds, represents an essential food constituent of high commercial value.[1] Noteworthy, (all-*rac*)-**1** is produced industrially on a multi 10.000 tons per year scale and mainly used in animal nutrition.[2] While all eight individual stereoisomers within this equimolar mixture are biologically active, the natural (*R*,*R*,*R*)-isomer (**1**) clearly exhibits the highest activity.[3] As the growing demand of isomerically pure **1** cannot be satisfied from the limited natural sources, the development of stereoselective (and scalable) syntheses of (*R*,*R*,*R*)-**1** represents a very important task. Pfaltz et al. have demonstrated that the side chain stereocenters can be established with impressive levels of selectivity through Ir-catalyzed asymmetric hydrogenation.[4] While several 2*R*-selective approaches towards **1** have been published,[5] for instance exploiting an organocatalytic chroman synthesis[5d] or a chiral sulfoxide-directed allylation step,[5b] the stereocontrolled set-up of the (*R*)-configured quaternary center C-2 in the frame of an efficient overall total synthesis of **1** still remains an open challenge.

Building on our interests in enantioselective 1,4-addition chemistry[6] we recently devised a novel strategy towards α-tocopherol (**1**) which involves the addition of a methyl-anion reagent to a chromenone precursor as the key stereogenic step (Scheme 1).[7] Employing substrates of type **3**, we achieved the Ni-catalyzed conjugate addition of $AlMe_3$ to afford the chromanone products of type **2** in high yield, however, only as a 1:1 mixture of the 2*R* and 2*S* stereoisomers. Remarkably, all attempts to perform the Ni-catalyzed reaction in an asymmetric fashion in the presence of chiral ligands remained completely unsuccessful, presumably because of a radical mechanism involved.[7]



Scheme 1. Retrosynthetic analysis of **1** based on an asymmetric 1,4-addition to a chromenone precursor.

While 2-substituted chromenones of type **3** were found not to react with $AlMe_3$ or MeMgBr in the presence of Cu^{I} catalysts under various conditions, we reasoned that an additional (disposable) electron-withdrawing group at C-3 (e.g., as in **4**) should enhance the reactivity of the substrates allowing to exploit a Cu-catalyzed asymmetric 1,4-addition[8] to generate the quaternary center stereoselectively. We here report the successful realization of this concept and its application as the key step in an efficient total synthesis of (*R*,*R*,*R*)-α-tocopherol (**1**).

At first, a suitable methodology for the preparation of activated substrates of type **4** had to be developed. Known protocols[9] for the synthesis of 2-alkyl-substituted chromenones bearing an ester group at C-3 could not be applied in our case due to the facile formation of the thermodynamically more stable 3-acylcoumarins. Also, various attempts to introduce an ester functionality by alkoxycarbonylation[10] of chromenones of type **3** or their 3-bromo derivatives failed. Nevertheless, the synthesis of the key substrate **4a** was finally achieved via vinyl ether formation and subsequent Friedel–Crafts acylation as shown in Scheme 2.

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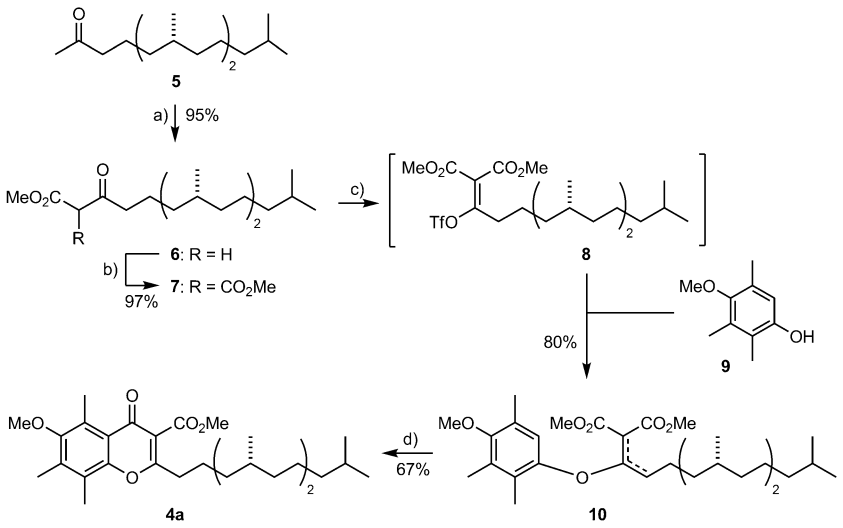


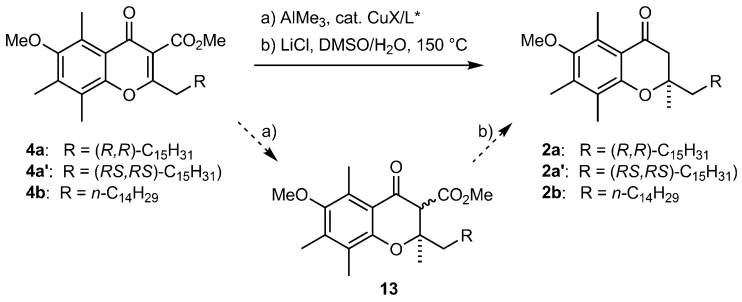
Scheme 2. Synthesis of the activated chromenone **4a**: a) $CO(OMe)_2$, NaH/KH, THF, reflux, 4 h; b) ClCOOMe, $MgCl_2$, pyridine, CH_2Cl_2, RT, 3 d; c) i) Tf_2O, NEt_3, 3 h, ii) **9**, Et_3N, CH_2Cl_2, RT, 5 d; d) Eaton's reagent, 55 °C, 1 h. Eaton's reagent = 7.7 wt% P_4O_{10} in $MeSO_3H$; Tf_2O = trifluoromethanesulfonic anhydride.

Starting from (*R*,*R*)-hexahydrofarnesyl acetone (**5**)[11] the β-ketoester **6** was prepared by reaction with dimethyl carbonate in the presence of KH/NaH.[12] While the conversion of **6** into the 2-acyl-malonate **7** could not be achieved with DBU-CO_2/MeI[13] we succeeded to perform this second methoxycarbonylation step in excellent yield by treatment of **6** with methyl chloroformate in the presence of $MgCl_2$ (as a coordinating agent) and pyridine as a base.[14] After in situ activation of the malonate **7** by *O*-sulfonylation and reaction of the resulting enol triflate **8** with the aromatic building block **9**[7] the aryl vinyl ether **10** was obtained as a mixture of double bond isomers.[15] The Friedel–Crafts-type cyclization of **10** to the activated chromenone **4a** was then achieved using Eaton's reagent (P_4O_{10} in $MeSO_3H$).[16]

For the optimization of the key 1,4-addition step we also prepared compound **4b** with an unbranched side chain as an achiral model substrate (Scheme 3). In this case, commercial palmitoyl chloride (**11**) was reacted with dimethyl malonate in the presence of NaH to afford the ketodiester **12** in excellent yield. The conversion of **12** into **4b** was then performed following the protocols used before in the preparation of **4a**.

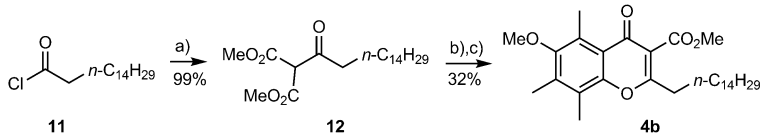
With the chromenones **4a** and **4b** in our hands we next investigated the key 1,4-addition (Scheme 4). Initial experiments with MeMgBr revealed that the 1,4-addition takes place even in the absence of a Cu^I catalyst at −78 °C and testing some chiral Cu^I complexes did not result in any chiral induction. Therefore, the study was continued employing $AlMe_3$ as a less reactive reagent. Because the stereochemical analysis was too difficult at the stage of the β-ketoesters of type **13** (mixture of diastereomers), the 1,4-addition products **13** were further converted into the chromanones of type **2** by demethoxycarbonylation under Krapcho conditions.[17] It was found that an excess (typically 35 equiv) of water is recommended, especially on a multi-mmol scale, to suppress a partial racemization of **2b** under the conditions of the Krapcho demethoxycarbonylation (LiCl, DMSO, 150 °C, 4 h) by securing a rapid protonation of the initially formed enolate.

We then tested various chiral ligands in the Cu^I-catalyzed reaction of the achiral substrate **4b** with $AlMe_3$ under standard conditions A (THF, −30 °C, dropwise addition of the chrome-



Scheme 4. a) Cu-catalyzed 1,4-addition of $AlMe_3$ to activated chromenones of type **4** with b) subsequent demethoxycarbonylation. For selectivities and yields, see Table 1.

none **4b** to the mixture of catalyst and $AlMe_3$)[18] using copper thiophenecarboxylate (CuTC) as the Cu^I source. The enantiomeric ratio of the product (**2b**/*ent*-**2b**) was determined by means of HPLC[19] after demethoxycarbonylation of intermediate **13**. Initially, various chiral P,P-ligands which had been successfully used in Cu-catalyzed asymmetric 1,4-additions[6,20] (e.g., ferrocene-based Taniaphos,[21] or Josiphos,[22] and Taddol-derived phosphine-phosphites[23]) were tested, however, no significant levels of conversion or enantioselectivity were observed. Likewise, the chiral

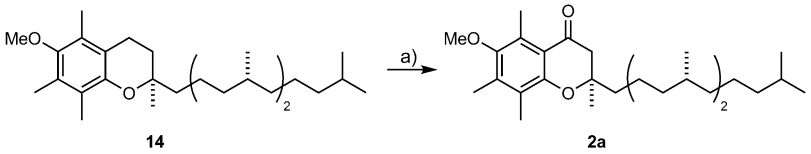


Scheme 3. Synthesis of the model substrate **4b**: a) NaH, dimethyl malonate, THF, RT, 5 h; b) Tf_2O, NEt_3, CH_2Cl_2, RT, 3 h, then **9**, Et_3N, RT, 2 d, 64%; c) Eaton's reagent, 55 °C, 3 h, 50%.

carbene ligand SIMes-leucinol[24] only afforded the racemic product (*rac*-**2b**; $\leq$2% *ee*). Next, we tested chiral phosphoramidite ligands, introduced by Alexakis for the enantioselective generation of quaternary stereocenters through 1,4-addition using aluminum reagents.[25] While a rapid conversion (TLC) but only a racemic product was observed with ligand **L1** (Table 1; entry 1) we obtained **2b** with a significant level of enantioselectivity (40% *ee*) for the first time using the BINOL-derived MonoPhos ligand **L2**.[26] The enantioselectivity was then optimized by systematic variation of the ligand structure, especially with respect to the substituents R^1 and R^2 at the nitrogen atom. Out of 35 MonoPhos-type phosphoramidites tested, the (commercially available)[27] *N*-methyl-*N*-benzyl-substituted ligand **L5** gave rise to the highest enantioselectivity (entry 3). With only 12 mol% of ligand at −50 °C (conditions B) the 1,4-addition proceeded with an improved yield and without loss of selectivity (entry 4). The subtle dependence of the reaction outcome on the ligand structure is exemplified by the drop of selectivity associated with the introduction of a single methyl group at the benzyl substituent (L7, entry 5).

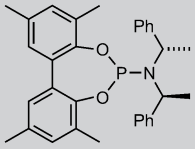
To our surprise, the substrate with the "natural", branched side chain (**4a**) yielded the product with a much lower degree of selectivity under the developed reaction conditions (entry 6). As a comparable (opposite) selectivity was found with the enantiomeric ligand *ent*-**L5** a significant matched/mismatched effect with respect to the configuration of the side chain stereocenters could be excluded (entries 6 and 7). Further experiments employing the stereochemically undefined substrate **4a**′ (mixture of four diastereomers) revealed that the selectivity could not be improved just by ligand variation. Eventually, it was found that a greatly improved stereoselectivity could be achieved by changing the copper source from CuTC to $(CuOTf)_2$·benzene[18,28] and the solvent from THF to Et_2O (conditions C). Much to our satisfaction, the reaction of **4a** proceeded smoothly under the optimized conditions (using ligand **L5**) even on a gram scale affording the desired chromanone **2a** in 83% isolated yield after demethoxycarbonylation with a stereoselectivity of 97:3 (2*R*/2*S*). The (2*R*)-configuration of the main diastereomer (**2a**) was confirmed by means of an authentic sample prepared independently from natural (*R*,*R*,*R*)-α-tocopherol (**1**) by *O*-methylation (→ **14**)[29] followed by PCC oxidation[30] (Scheme 5).

Finally, completion of the synthesis was achieved by Pd-catalyzed hydrogenolysis of the keto function of chromanone **2a**, affording *O*-methyl-α-tocopherol in 97% yield, which had been previously converted to α-tocopherol (**1**) by Lewis acid-induced cleavage of the methyl ether functionality[5d] (Scheme 6).

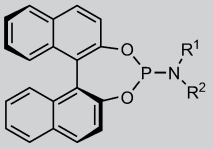


Scheme 5. Preparation of an authentic sample of the (2*R*)-configured 1,4-addition product **2a** for characterization purposes. a) PCC, CH_2Cl_2, reflux, 3 d, 53%.

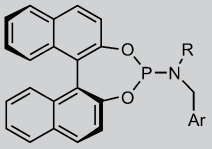
Table 1. Performance of various phosphoramidite ligands in the Cu-catalyzed 1,4-addition of $AlMe_3$ to chromenone substrates according to Scheme 4.



L1



L2: $R^1 = R^2 = Me$
L3: $R^1 = Me$; $R^2 = n$Pr
L4: $R^1 = Me$; $R^2 = Ph$

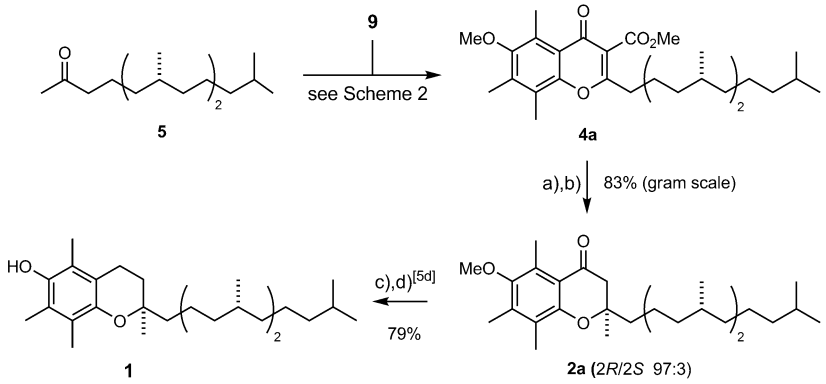


L5: R = Me, Ar = Ph
L6: R = Et, Ar = Ph
L7: R = Me, Ar = *o*-tol

Entry	Conditions[a]	Substrate	Ligand	2*R*/2*S*[b]	Yield [%][c]
1	A	**4b**	**L1**	50:50	n.d.
2	A	**4b**	**L2**	70:30	n.d
3	A	**4b**	**L5**	97:3	76
4	B	**4b**	**L5**	98:2	94
5	A	**4b**	**L7**	89:11	n.d.
6	A	**4a**	**L5**	79:21	n.d.
7	A	**4a**	*ent*-**L5**	22:78	n.d.
8	A	**4a**′	**L5**	80:20	n.d.
9	A	**4a**′	**L4**	no conversion	
10	A	**4a**′	**L6**	no conversion	
11	C	**4a**′	**L3**	89:11	n.d.
12	C	**4a**′	**L5**	95:5	n.d.
13	C	**4a**	**L5**	97:3	83

[a] A: CuTC (10 mol%), ligand (20 mol%), $AlMe_3$ (2 equiv), THF, −30 °C, overnight; B: CuTC (10 mol%), ligand (12 mol%), $AlMe_3$ (2 equiv), THF, −50 °C, overnight; C: $(CuOTf)_2$·benzene (5 mol%), ligand (12 mol%), $AlMe_3$ (2 equiv), Et_2O, −50 °C, overnight. [b] Determined by means of HPLC (after demethoxycarbonylation). [c] Isolated yield of chromanone **2** over 2 steps.

In conclusion, we have successfully developed a conceptually novel (2*R*)-selective total synthesis of α-tocopherol (**1**) by exploiting a catalytic and stereoselective 1,4-addition as a key step (**4a** → **2a**). The synthesis requires only eight steps (33% overall yield) starting from (*R*,*R*)-hexahydrofarnesyl acetone (**5**) as an industrially accessible compound. Moreover, we could demonstrate that Cu-catalyzed 1,4-additions to particularly unreactive 2-substituted chromenones can be achieved with high levels of catalyst-directed stereocontrol by introduction of a removable activating ester substituent at C-3.



Scheme 6. Completion of the developed synthesis of α-tocopherol (**1**). a) $(CuOTf)_2$·benzene (5 mol%), **L5** (12 mol%), $AlMe_3$ (2.0 equiv), Et_2O, −50 °C, 18 h; b) LiCl (3.0 equiv), H_2O (35 equiv), DMSO, 150 °C, 5 h; c) H_2 (balloon), Pd/C, AcOH, 60 °C, 96 h; d) $AlCl_3$, BF_3·Et_2O, MeCN, RT, 6 h (see ref. [5d]).

Keywords: asymmetric conjugate addition · copper catalysis · chiral ligands · chromenones · vitamin E

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