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SHORT COMMUNICATION

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Total Synthesis of (2*RS*)-α-Tocopherol through Ni-Catalyzed 1,4-Addition to a Chromenone Intermediate

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A novel strategy for the total synthesis of α-tocopherol ("vitamin E") was elaborated on the basis of the conjugate addition of $AlMe_3$ (as a methyl anion equivalent) to a 2-substituted chromenone. Starting from trimethylhydroquinone and (*R*,*R*)-hexahydrofarnesol, the required chromenone substrate was efficiently prepared in a short sequence exploiting a $TiCl_4$-mediated Fries rearrangement and a KO*t*Bu-induced Baker–Venkatamaran rearrangement. The envisioned key step, which sets up the quaternary center at C2, was performed in virtually quantitative yield through Ni-catalyzed conjugate addition of $AlMe_3$. However, this transformation, which likely proceeds through a radical mechanism, could not be rendered stereoselective by means of chiral ligands. Nevertheless, the elaborated synthesis of (2*RS*,4′*R*,8′*R*)-α-tocopherol (2-*ambo*-α-tocopherol) is efficient and challenges the future development of suitable protocols for the asymmetric 1,4-addition.

Introduction

Vitamin E is an essential food ingredient of high economical value owing to its biological activity and antioxidant properties.[1] The commercially most important form is (*all-rac*)-α-tocopherol (*all-rac*-**1**), which is produced on a scale of >35000 t year^{-1} and mainly applied in animal nutrition.[2] Although the eight individual stereoisomers of this equimolar mixture exhibit qualitatively the same biological activity, the (*R*,*R*,*R*)-**1** is the only naturally occurring compound that also shows the highest bioactivity.[3] As the growing demand of this single-isomer product cannot be satisfied through natural sources, the development of scalable and stereoselective syntheses of **1** represents an important research goal.[4] Whereas the stereocenters of the side chain can be established with an impressive level of stereocontrol through asymmetric hydrogenation,[5] the (*R*)-selective generation of the quaternary stereocenter at C2 still remains a tough challenge.[6]

In continuation of our recent work in the field of enantioselective 1,4-addition,[7] we devised a new approach towards vitamin E in which the methyl group at C2 is introduced through metal-catalyzed 1,4-addition to a chromenone precursor. We reasoned that this key step could possibly be conducted stereoselectively in the presence of a chiral ligand.[8] We herein disclose the results of a study, which so far has culminated in the elaboration of an efficient synthesis of 2-*ambo*-α-tocopherol [(2*RS*)-**1**].

Results and Discussion

In our retrosynthetic analysis (Scheme 1), ketone **2** serves as a pretarget molecule, which results from conjugate addition of a methyl-metal reagent to chromenone **3**. This intermediate in turn could be assembled from *ortho*-hydroxy acetophenone derivative **4** and acid **5**. Aromatic building block **4** is derived from commercially available trimethylhydroquinone (**6**, TMHQ) through regioselective *O*-methylation and *C*-acetylation (possibly through Fries rearrangement).[9] Side-chain building block **5** could be prepared under C_2 chain elongation from hexahydrofarnesol (**7**). For the protection of the phenol function, we selected a methyl ether because of its stability and because of the availability of an efficient deprotection protocol for *O*-methyltocopherol.[10]

The preparation of acetophenone building block **4** (Scheme 2) required the differentiation of the two OH groups of **6**, which was achieved by pivaloylation.[11] The remaining phenol function of **8** was then methylated (NaH, Me_2SO_4) before alkaline ester hydrolysis and subsequent acetylation of the phenol intermediate (AcCl, pyridine) afforded acetate **9** (85% overall from **6** on a 100 scale). An initial attempt to perform the Fries rearrangement of **9** by using $BF_3{\cdot}OEt_2$[12] failed, because of concomitant cleavage of the methyl ether. However, after screening various Lewis acids and conditions we succeeded in effectively achieving

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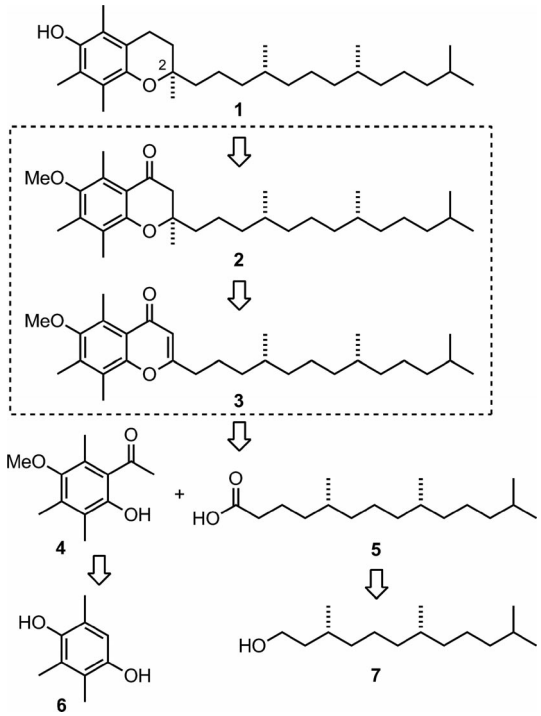
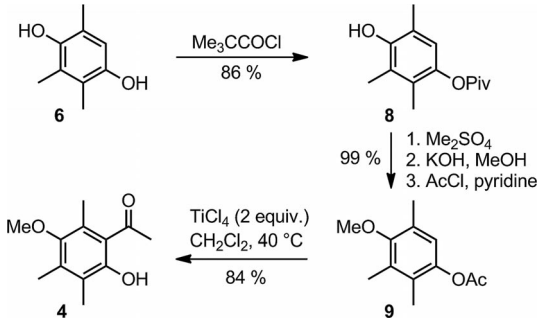


Scheme 1. Retrosynthetic analysis of α-tocopherol (**1**) by using 1,4-addition to generate the quaternary C2 center.

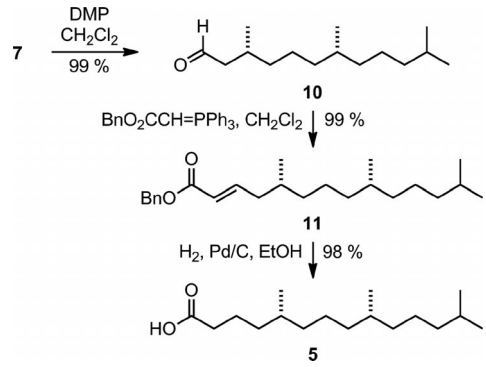
the desired transformation by using $TiCl_4$ in refluxing CH_2Cl_2 over 3 d. The sequence shown in Scheme 2 offers reliable access to acetophenone **4** on a multigram scale.



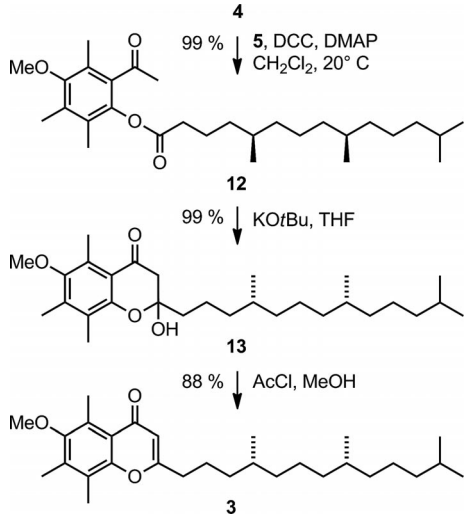
Scheme 2. Preparation of aromatic building block **4**.

The synthesis of side-chain building block **5** (Scheme 3) started with Dess–Martin oxidation[13] of (*R*,*R*)-hexahydrofarnesol (**7**)[14] followed by immediate olefination of aldehyde **10** by using the Wittig reagent obtained from benzyl bromoacetate. Hydrogenation of resulting enoate **11** (H_2, Pd/C, EtOH) then proceeded smoothly under additional hydrogenolytic ester cleavage to afford **5** in high overall yield (96% over three steps).

The assembly of key intermediate **3** (Scheme 4) was initiated by connecting building blocks **4** and **5** by ester formation under Steglich conditions.[15] Treatment of a THF solution of resulting ester **12** with KO*t*Bu as a base smoothly afforded hemiacetal **13** (Baker–Venkatamaran rearrangement),[16] which was then dehydrated under acidic conditions (AcCl, MeOH) to give chromenone **3** in high overall yield.

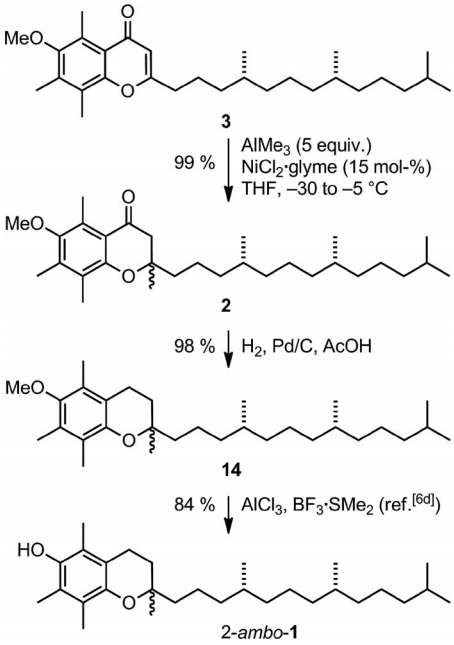


Scheme 3. Synthesis of side-chain building block **5**; DMP = Dess–Martin periodinane.



Scheme 4. Assembly of key intermediate **3** from building blocks **4** and **5**; DCC = *N*,*N*′′-dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

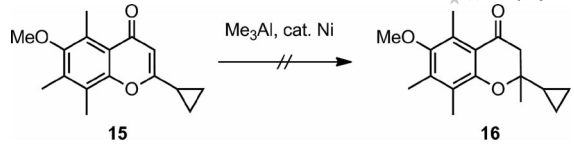
With chromenone **3** in hand, we next turned our attention to the key 1,4-addition. Initial attempts to react **3** with MeMgBr or Me_3Al in the presence of different Cu^I catalysts failed completely.[17] However, the reaction of **3** with Me_3Al in the presence of Ni^{II} salts[18] afforded the desired product (Scheme 5). Under the optimized conditions (using 5 equiv. of Me_3Al in the presence of 15 mol-% of $NiCl_2$·glyme), 4-oxo-α-tocopheryl methyl ether (**2**) was obtained in virtually quantitative yield as a 1:1 mixture of diastereomers. Hydrogenolytic removal of the benzylic keto functionality (H_2, Pd/C) then afforded α-tocopheryl methyl ether (**14**). The final deprotection of the aryl methyl ether is known to proceed with BF_3·SMe_2/$AlCl_3$ according to Woggon et al., which furnished 2-*ambo*-α-tocopherol (2-*ambo*-**1**) in high yield.[6d,10]



Scheme 5. Completion of the synthesis of 2-*ambo*-**1**.

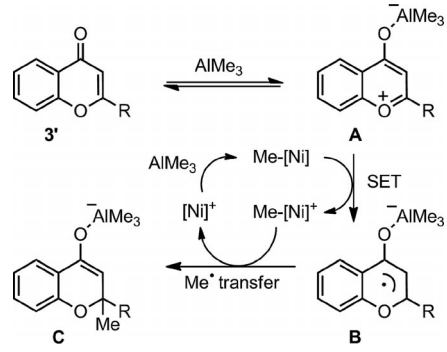
Having completed the total synthesis of 2-*ambo*-α-tocopherol (2-*ambo*-**1**), we next investigated the possibility to perform the key 1,4-addition stereoselectively in the presence of a chiral Ni complex. However, despite extensive experimentation this goal could not be achieved. Besides chiral ferrocenyl ligands (Taniaphos, Mandyphos, and Josiphos),[19] we tested different phosphoramidites,[20] modular phosphine–phosphites,[21] box ligands,[22] as well as chiral amines and amino alcohols. However, we never observed any significant degree of asymmetric induction (<2%*de* according to HPLC analysis). Epimerization of the product at C2 under the reaction conditions could be excluded by means of a reference sample obtained through HPLC separation of the diastereomers of (*2RS*)-**2**. However, the presence of the Ni catalyst was required for the 1,4-addition to proceed. The complete lack of asymmetric induction suggested that the stereodefining C–C bond-forming step did not take place in the expected fashion (i.e., by reductive elimination from the chirally ligated Ni center). To probe whether the reaction possibly proceeded through a radical mechanism, we synthesized cyclopropyl-substituted substrate **15**[23] and subjected it to the established conditions (Scheme 6). Noteworthy, we did not observe the formation of 1,4-addition product **16** in this case. Instead, a complex mixture was formed that showed olefinic signals in the ^{1}H NMR spectrum.

The above-mentioned experiment suggested that the Ni-catalyzed 1,4-addition of $AlMe_3$ to the chromenone substrates indeed proceeded via a (delocalized) radical intermediate. A possible mechanism is shown in Scheme 7. As an excess amount of $AlMe_3$ is required, we assume that the reaction starts with the formation of 4-oxybenzopyrylium species **A**,[24] which accepts an electron from a low-valent methyl nickel complex (single-electron transfer). This leads



Scheme 6. Attempted Ni-catalyzed 1,4-addition of Me_3Al to cyclopropyl-substituted chromanone **15**.

to the proposed (highly stabilized) radical intermediate **B**, to which the methyl group is then delivered in a fast radical-transfer reaction. This C–C bond-forming step is not expected to proceed stereoselectively under the influence of (rather remote) chiral ligands at the nickel center. Resulting enolate intermediate **C**, which should be configurationally stable (see above), is then converted into the chromanone product during aqueous workup.



Scheme 7. Proposed mechanistic pathway (only the core structure of substrate **3** is shown for clarity). SET = single-electron transfer.

Conclusions

In conclusion, we devised a new strategy for the synthesis of tocopherols and elaborated an efficient total synthesis of 2-*ambo*-α-tocopherol (2-*ambo*-**1**) proceeding with an overall yield of >60% over nine steps starting from (*R*,*R*)-hexahydrofarnesol (**7**). As a key step, we exploited a high-yielding Ni-catalyzed 1,4-addition of $AlMe_3$ to a chromenone substrate as a novel option to build up the quaternary center at C2. Noteworthy, this reaction could not be rendered stereoselective by means of chiral ligands, probably because of the radical nature of the C–C bond-forming step. This failure might be an important lesson also to other researchers working in the field of low-valent Ni catalysis and challenges future methodology development. In any case, the facile formation of radical intermediates by single-electron reduction of 2-substituted chromenones must be taken into account in any future attempts to exploit an asymmetric 1,4-addition strategy in the synthesis of vitamin E or related natural products.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra of all relevant compounds.

Acknowledgments

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[14] For the synthesis of (*R*,*R*)-**7** [93.45% (3*R*,7*R*); 5.81% (3*R*,7*S*); 0.75% (3*S*,7*R*); <0.1% (3*S*,7*S*)] see ref.[5a,5c]

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[23] Compound **15** was prepared from **4** and cyclopropanecarbonyl chloride in analogy to the synthesis of **3**.

[24] Treatment of a related chromenone with an unbranched *n*-$C_{15}H_{31}$ side chain in [D_8]THF with Me_3Al (3 equiv.) led to a downfield shift of the olefinic ^1H NMR signal (H3) by 0.5 ppm. This supports structure **A**.

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