Preparation of Enantiopure Precursors for the Vitamin E Synthesis. A Comparison of the Asymmetric Allylation of Ketones and the Sharpless Bishydroxylation

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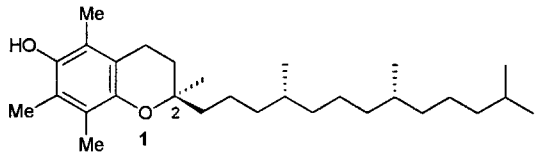
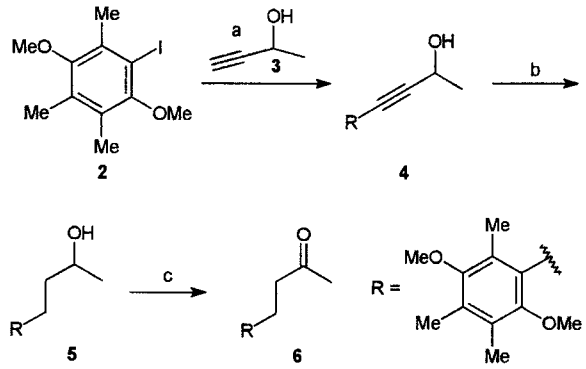
Abstract: The enantioselective synthesis of the precursors **9**, **10**, **16** and **17** for the preparation of enantiopure vitamin E by asymmetric allylation of the ketone **6** and Sharpless bishydroxylation of the aliphatic alkenes **11** and **15** is described.

The enantioselective generation of the stereogenic center C-2 in the chromane skeleton of vitamin E (α-tocopherol) **1** with a tertiary ether moiety is a crucial step in the total synthesis of this important vitamin. The first synthetic approaches aiming at this goal were based on optical resolution[1] as well as the use of enantiopure natural substrates.[2] Recently, auxiliary controlled reactions[3] and asymmetric oxidations[4] have been reported. In this paper we describe the synthesis of two vitamin E precursors using a new method which has been developed in our group and allows the formation of tertiary ethers with good to excellent induced selectivity by allylation of alkyl methyl ketones.[5] In addition we compare this method with other procedures applicable to the enantioselective synthesis of vitamin E such as the Sharpless bishydroxylation.[6]

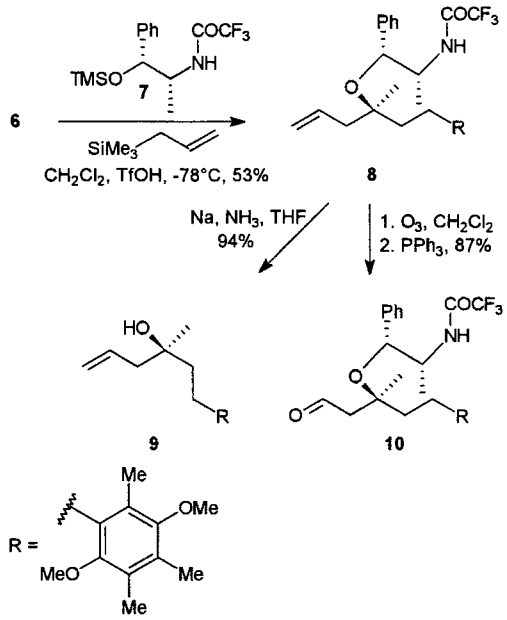


As a substrate for the allylation, the ketone **6** was prepared starting from readily available **2**[7] which was transformed into **4** by a *Sonogashira*-coupling[8] with the ynol **3** followed by hydrogenation (Pd/C/H_2) and oxidation with Dess-Martin periodinane[9] to give **6** via **5**.

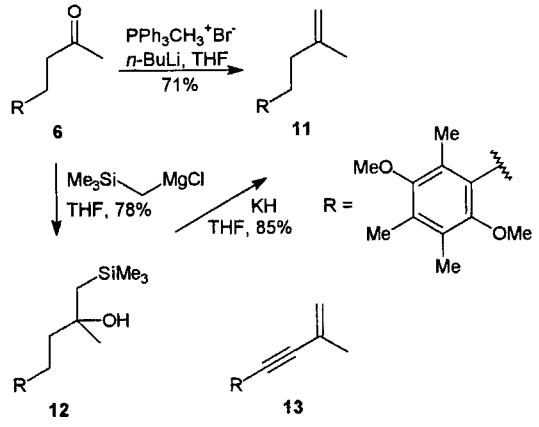


a: $Pd(PPh_3)_2Cl_2$, CuI, $HNEt_2$, 67%; b: Pd/C, MeOH, 3 bar H_2, 96%;
c: Dess-Martin periodinane, CH_2Cl_2, 89%

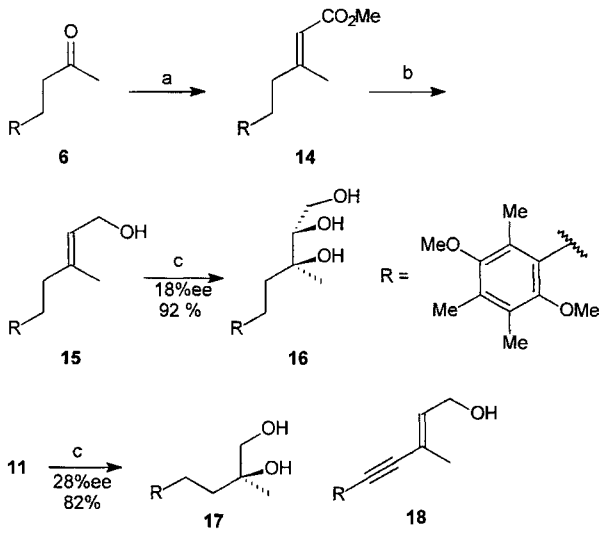
Reaction of **6** with allylsilane and the norpseudoephedrine derivative **7** in the presence of a catalytic amount of trifluoromethanesulfonic acid directly led in a domino type transformation[5,10] to **8**[11] with 53% yield (78% based on turnover). At this point it should be noted that the purity of the trifluoromethanesulfonic acid is of crucial importance. Usually the purchased TfOH as employed in this experiment seems not to be sufficient. Newer investigations of this reaction have revealed that trifluoromethanesulfonic acid obtained by *in situ* hydrolysis of trimethylsilyl trifluoromethanesulfonate gives the best results with yields >90%. The diastereoselectivity of the transformation was 9:1 as determined by ^{1}H-NMR and ^{13}C-NMR. Deprotection of the homoallylic ether in **8** with sodium in liquid ammonia proceeds selectively without Birch reduction of the aromatic moiety to give the corresponding alcohol **9**[12] in almost quantitative yield. The arene is also stable to ozonolysis; thus, treatment of **8** with ozone furnished aldehyde **10**[13] in 87% yield. Vitamin E may be obtained from **9** by cyclization after oxidative demethylation, rearomatisation and further transformations according to known procedures or it can be formed from **10** after attachment of the side chain, deprotection and transformations as above.



For the sake of comparison we have also transformed ketone **6** into alkene **11** which was subjected to Sharpless bishydroxylation. To ensure that the enantioselectivity of this reaction is not influenced by any impurities of the starting material, we prepared **11** by two different routes, namely by methylenation of **6** in a Wittig reaction in 71% yield and by a Grignard reaction of **6** with trimethylsilylmethylmagnesium chloride to give the alcohol **12** (78%) which underwent Peterson elimination[14] on treatment with potassium hydride in 85% yield.



Ketone **6** was also transformed into the allylic alcohol **15** as a second substrate for the enantioselective bishydroxylation by reaction with trimethylphosphonoacetate followed by reduction with DIBAH in 77% overall yield. The bishydroxylation of the two alkenes **11** and **15** was performed under standard conditions (*t*-BuOH, H_2O, AD-Mix-α, $[(DHQ)_2PHAL]$, 8-24h, 4°C). The diol **17**[4] and triol **16**[15] were obtained in good yields but unexpectedly low enantioselectivities (29% and 18% ee) which were determined using the Mosher ester[16] method (^1H and ^{19}F). These results were unexpected since the enynes **13** and **18** show a good to excellent selectivity in the bishydroxylation (84%ee and >95%ee) under the same conditions. Thus, we assume that in contrast to the slim arylalkynyl group in **13** and **18** the bulky arylalkanyl group in **11** and **15** does not fit into the pocket of the catalyst and therefore does not allow a high facial discrimination of the alkene moiety in these compounds. This finding is underlined by force field calculations which show a staggered conformation of the arylalkanyl group in **11** and **15**. A survey of the literature[17] revealed that alkenes of the type encountered in **11** and **15** are poor substrates for the Sharpless bishydroxylation, especially in cases with *ortho* substituents.



a: LiHMDS, THF, $(MeO)_2P(O)CH_2CO_2Me$, 83%; b: DIBAH, THF, 93%; c: *t*-BuOH, H_2O, AD-Mix-α, $[(DHQ)_2PHAL]$

The results clearly demonstrate that the Sharpless bishydroxylation of alkenes as **11** and **15** is not suitable for the formation of enantiopure precursors for the synthesis of vitamin E. In contrast the direct allylation of ketone **6** using our method allows the selective formation of appropriate precursors as **9** and **10**.

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References and Notes

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(11) ^1H-NMR (200 MHz): **8**: δ = 0.99 (s, 3H), 1.25 (d, *J* = 7 Hz, 3H), 1.53-1.73 (m, 2H), 2.17 (s, 9H), 2.46 (d, *J* = 7 Hz, 2H), 2.61-2.80 (m, 2H), 3.64 (s, 3H), 3.65 (s, 3H), 4.09-4.20 (m, 1H), 4.68 (d, *J* = 4 Hz, 1H), 5.11-5.22 (m, 2H), 5.80-5.96 (m, 1H), 6.49 (d, *J* = 7 Hz, 1H), 7.23-7.36 (m, 5H).

(12) ^1H-NMR (200 MHz): **9**: δ = 1.26 (s, 3H), 1.56-1.68 (m, 2H), 2.16 (s, 3H), 2.19 (s, 3H), 2.30 (d, *J* = 7 Hz, 2H), 2.64-2.77 (m, 2H), 3.64 (s, 3H), 3.70 (s, 3H), 5.07-5.19 (m, 2H), 5.80-6.03 (m, 1H).

(13) ^1H-NMR (500MHz): **10**: δ = 1.17 (d, *J* = 6.2 Hz, 3H), 1.23 (s, 3H), 1.75 (t, *J* = 8.3 Hz, 2H), 2.11 (s, 3H), 2.15 (s, 3H), 2.16 (s, 3H), 2.58-2.71 (m, 2H), 2.75 (d, *J* = 2.4 Hz, 2H), 3.62 (s, 3H), 3.63 (s, 3H), 4.13-4.22 (m, 1H), 4.69 (d, *J* = 5.0 Hz, 1H), 6.42 (d, *J* = 8 Hz, 1H), 7.23-7.35 (m, 5H).

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(15) ^1H NMR (300 MHz): **16**: δ = 1.24 (s, 3H), 1.71 (m_c, 2H), 2.16 (s, 6H), 2.22 (s, 3H), 2.66 (m_c, 3H), 2.80 (br. s, 1H), 3.11 (br. s, 1H), 3.65 (s, 3H), 3.72 (s, 3H), 3.79 (d, *J* = 7 Hz, 2H).

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