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# Diastereoselective Synthesis of α-Tocopherol: A New Concept for the Formation of Chromanols

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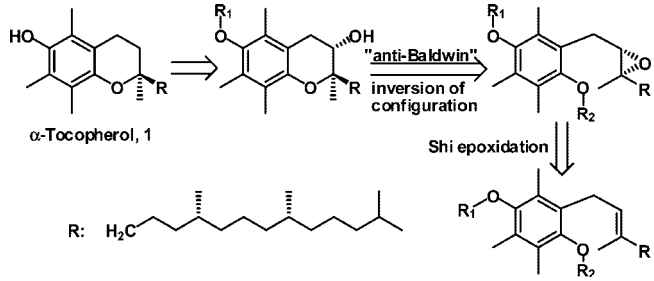
## ABSTRACT

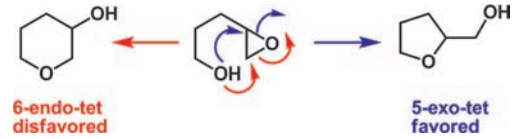



**A diastereoselective synthesis of α-tocopherol 1 (93% de) was achieved via two key steps, (i) a highly diastereoselective Shi epoxidation of a trisubstituted alkene and (ii) an acid supported, "anti-Baldwin" epoxide ring opening under inversion of configuration leading to the 6-membered chromanol ring.**

In the vitamin E family, α-tocopherol **1** is the biologically most active member regarding radical-chain-breaking antioxidant ability in tissues.[1,2] Although isolation and characterization of vitamin E chromanols and their biosynthesis[3] have been widely described, the stereoselective total synthesis of **1** still remains rare.[4,5] We recently published a biomimetic synthesis of **1**,[6] based on the mechanism of chromanol formation as catalyzed by the enzyme tocopherol cyclase from *Cyanobacteria*, and a highly stereoselective synthesis induced by a domino aldol/oxa-Michael reaction.[7] Herein, we report an alternative strategy involving two key steps, i.e., a stereoselective Shi epoxidation, followed by an "anti-Baldwin" epoxide ring opening under inversion of configuration.

In general, γ-epoxy alcohols preferably cyclize to furans obeying rules published by Baldwin in 1976[8] (Scheme 1).

**Scheme 1.** Baldwin Rules for γ-Epoxy Alcohol Cyclizations

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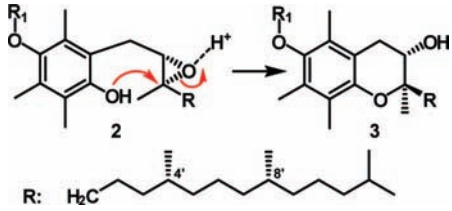
In the past two decades, several methods aimed at circumventing these rules in order to favor the formation of pyrans have been published. However, most of these approaches required either the modification of the epoxide substrate by covalently attached directing groups[9] or the use of transition-metal complexes[10] or antibody catalysts.[11]

Recently, Jamison et al. reported an epoxide-opening cascade for the construction of ladder polyether marine natural products.[12] Under optimized conditions in water at pH = 7.0, a ratio of 11:1 in favor of the pyran product was accomplished. Though the epoxy alcohols used in this study are templated toward pyran formation, we were encouraged to envisage chromanol formation via an epoxide ring opening as depicted in Scheme 2.

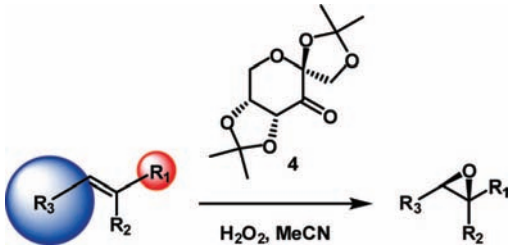
**Scheme 2.** Proposed Chromanol Ring Construction[a]




[a] In all schemes, figures and tables, R = (4′*R*,8′*R*)-4′,8′,12′-trimethyltridecanyl.

First of all, this strategy requires the asymmetric epoxidation of a trisubstituted, unfunctionalized olefin. The stereoselective synthesis of epoxides has been extensively investigated[13] including the direct asymmetric epoxidation of alkenes.[14] But most of these methods are substrate dependent and hence were not considered to be suitable for our strategy. In 1997, Shi et al. reported the use of a chiral fructose-derived catalyst in the epoxidation of trans disubstituted and trisubstituted olefins[15,16] (Scheme 3). The wide

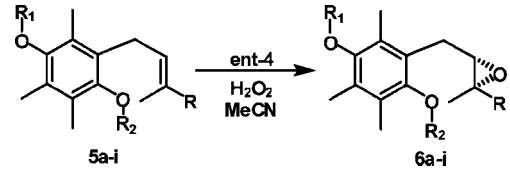
**Scheme 3.** Shi Epoxidation in MeCN Using $H_2O_2$ as a Co-oxidant




scope of reactive olefin substrates made it the catalyst of choice.

Several factors govern the selectivity of this reaction; in particular, the size of the olefin substituents is significant such that small $R_1$ and large $R_3$ groups gave the best enantioselectivities.[15] Further, Shi's mechanism-based correlation[15] between catalyst configuration and product stereochemistry suggested that we could obtain the desired epoxide **2** using **ent-4** rather than the commercially available **4**.[17] In view of the given structure of our synthetic intermediate **5**, variation of the protecting groups at the hydroquinone was the only choice to enhance the difference in size of the substitutents at the trisubstituted double bond.

**Table 1.** Shi Epoxidation of Olefins **5a**−**i**[a]




| entry | epoxide | $R_1$ | $R_2$ | yield[b] (%) | de[c] (%) |
|---|---|---|---|---|---|
| 1 | **6a** | (−)-Camph[d] | TBS | 73 | 79 |
| 2 | **6b** | TIPS | MOM | 62 | 66 |
| 3 | **6c** | TIPS | TBS | 76 | 73 |
| 4 | **6d** | TIPS | TIPS | 75 | 82 |
| 5 | **6e** | Me | TIPS | 78 | 85 |
| 6 | **6f** | Me | benzyl | 87 | 73 |
| 7 | **6g** | (−)-Camph[d] | Anthr[e] | 76 | 74 |
| 8 | **6h** | DPS | DPS | 81 | 91 |
| **9** | **6i** | **Me** | **DPS** | **81** | **97** |

[a] General experimental conditions: 1 equiv of **5**, 0.4 equiv of **ent-4**, and 5.4 equiv of $H_2O_2$ (30% aq) in a buffered (2 M $K_2CO_3$/EDTA) mixture of MeCN/EtOH/$CH_2Cl_2$ (1:1:2) at 0 °C for 10 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] (−)-Camphanoyl. [e] 9-Methylanthracenyl.


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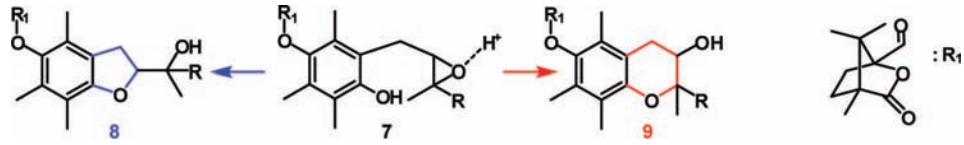
**Table 2.** Acid-Supported Reactions of Hydroxy Epoxides To Yield Various Ratios of Furan and Pyran Products[a]




| entry | acid (A) | solvent (S) | conv[b] (%) | ratio **8**:**9**[b] | entry | acid (A) | solvent (S) | conv[b] (%) | ratio **8**:**9**[b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | none | MeOH | 99 | 98:2 | 12[c] | TFA (20% mol) | $CH_2Cl_2$ | 99 | 72:28 |
| 2 | 1 N $HCl_{aq}$ | MeCN | 94 | 51:49 | 13[c] | (+)-CSA (1 equiv) | MeCN:$H_2O$ (3:1) | 99 | 47:53 |
| 3 | 1 N $HCl_{aq}$ | THF | 90 | 67:33 | 14[c] | (+)-CSA (0.5 equiv) | MeCN | 99 | 40:60 |
| 4 | 1 N $HCl_{aq}$ | MeOH | 92 | 56:44 | 15[c] | (+)-CSA (1 equiv) | MeCN | 99 | 40:60 |
| 5 | 1 N $HCl_{aq}$ | acetone | 92 | 58:42 | 16[c] | (+)-CSA (2 equiv) | MeCN | 99 | 38:62 |
| 6 | 1 N $HCl_{aq}$ | PC[d] | 97 | 51:49 | 17 | 2 M $HCl_{MeOH}$ | MeOH | 98 | 62:38 |
| 7 | 1 N $HCl_{aq}$ | DMF | 90 | 57:43 | 18 | 2 M $HCl_{Et2O}$ | $CH_2Cl_2$ | 92 | 54:46 |
| 8 | 1 N $HCl_{aq}$ | $CH_2Cl_2$ | 95 | 80:20 | 19 | 0.5 M $HCl_{Et2O}$ | MeCN | 95 | 26:74 |
| 9 | 6 N $HCl_{aq}$ | MeCN | 92 | 35:65 | 20 | 1 M $HCl_{Et2O}$ | MeCN | 97 | 26:74 |
| 10 | 12 N $HCl_{aq}$ | MeCN | 94 | 37:67 | **21** | **2 M $HCl_{Et2O}$** | **MeCN** | **98** | **23:77** |
| 11[c] | TFA (20% mol) | MeCN:$H_2O$ (3:1) | 99 | 49:51 | | | | | |

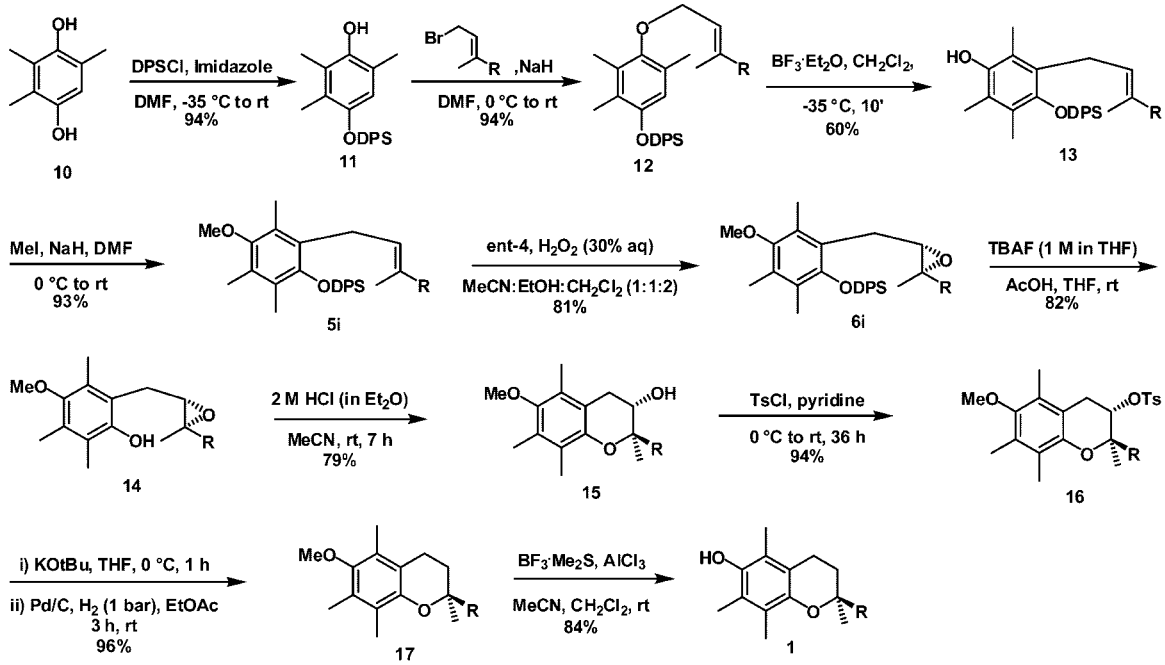
[a] General experimental conditions: 5 $\mu$mol of **7**, 1 mL of a S:A (3:1) mixture, rt, 15 h. [b] Determined by HPLC, unidentified side products were <1% in each case. [c] Reaction carried out at 50 °C for 15 h in a sealed tube. [d] Propylene carbonate.

Accordingly, we prepared a number of bis-protected phytyl hydroquinones **5a**−**i** which were converted to the corresponding epoxides **6a**−**i** in moderate to good yields, using catalyst **ent-4** (Table 1).

Screening of these substrates gave one outstanding result (entry 9) revealing that a small $R_1$ group (Me) and a large $R_2$ substituent (DPS, *tert*-butyldiphenylsilylether) are required to accomplish "remote control" on the diastereoselectivity of the Shi epoxidation. Note that background epoxidation is below 2% in the absence of chiral ketone.[16b]

In order to optimize the transformation of an epoxide such as **2** to the chromanol **3** (Scheme 2) compound **7** was used under various conditions (Table 2). Note that the epoxide of **7** is racemic at the epoxide and that the (−)-camphanate ester was chosen because all isomers of **8** and **9** are separable on HPLC. First, we employed the conditions reported by Jamison et al.,[12] which favored pyran products in MeOH. Cyclization of **7** in MeOH, at 50 °C, formed the furan product **8** almost exclusively (entry 1), following Baldwin rules. The best regioselectivity in favor of **9** was achieved when a

**Scheme 4.** Synthesis of α-Tocopherol **1**



mixture of acetontitrile and 2 M HCl in diethylether was used (entry 21). These conditions were selected to complete the synthesis of α-tocopherol **1** (Scheme 4).

Selective protection of **10** at the less hindered phenol,[18] followed by coupling of phytyl bromide, gave **12** in excellent yields. Lewis acid mediated double Claisen-rearrangement,[19] and protection of the resulting phenol, afforded olefin **5i** (>98:2, *E*/*Z*), subsequently oxidized according to Shi, to yield **6i** in 81% yield, and 97% de. Removal of the DPS protecting group of **6i** under usual conditions (TBAF, THF) gave only the 5-membered ring product. A slight modification of the procedure, described by Barett et al.,[20] overcame the problem, and **14** was isolated in 82% yield. Nucleophilic attack at the oxirane using our optimized conditions (entry 21, Table 2) was quantitative, affording **15** (93% de) in 79% yield and 19% of the product corresponding to **8**.

2D NOESY NMR experiments of **15** revealed only a weak NOE between $CH_3$ at C2 and H at C3 (Figure 1), versus a strong NOE between protons at C1′ and H at C3, indicating a trans relationship of the hydroxy group and the side chain, i.e., *R* configuration at C2 of the major isomer. This result was confirmed by separation of all four diastereoisomers on chiral HPLC (see the Supporting Information). Finally, removal of the hydroxy group went smoothly through the tosylate **16**, which was easily eliminated and directly hydrogenated to afford **17** in almost quantitative yield.

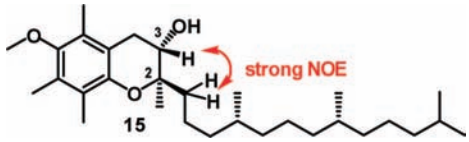



**Figure 1.** NOESY experiment of **15**.

Note that the small decrease of de from **6i** to **17** is due to the extent of carbenium ion formation during the conversion of **14** to **15**. Direct reductive cleavage of **16** using hydrides was not successful, as already reported by Stocker et al.[3a] Deprotection of the methyl ether could be performed without any loss of chirality, by means of $BF_3$•$Me_2S/AlCl_3$,[7] giving α-tocopherol **1**.

In summary, we developed a highly diastereoselective synthesis of α-tocopherol employing as key steps a Shi epoxidation and a carefully controlled intramolecular epoxyde opening and simultaneous cyclization to the "anti-Baldwin" product, that is, the chromanol ring of **1**.

**Acknowledgment.** We thank the Swiss National Science Foundation for financial support and Dr. T. Netscher (DSM) for a generous sample of natural phytol.

**Supporting Information Available:** Experimental procedures, complete spectroscopic data, chromatograms of compounds **6i**, **15**, and **17**, and $^1H$ and $^{13}C$ NMR spectra of compounds **5i**, **6i**, and **11**−**17** are documented. This material is available free of charge via the Internet at http://pubs.acs.org.

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