

[C0035]

Efficient Preparation of (2*R*,4'*R*,8'*R*)- α -Tocopherol by Hydroxymethylation

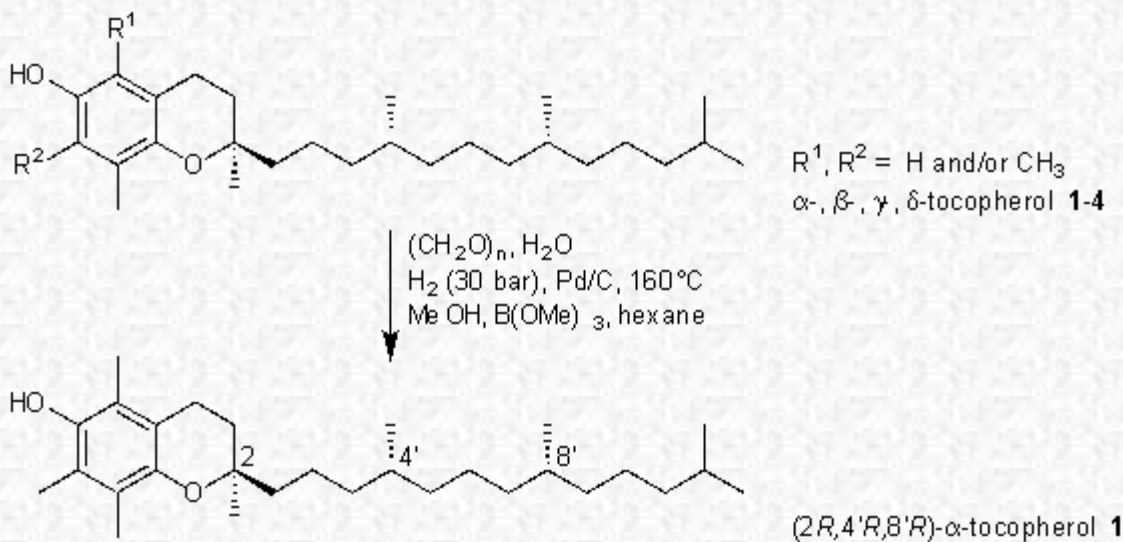
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(2*R*,4'*R*,8'*R*)- α -Tocopherol (**1**), the compound with highest vitamin E activity and, therefore, the biologically most valuable tocopherol, plays an important role in feed, food, and pharma industry. Since an economical total synthesis is not feasible up to now, large-scale production by semi-synthesis starts from natural-source material.¹ A mixture of α -, β -, γ -, and δ -tocopherol (**1-4**) can be obtained from soybean deodorizer distillates (originally a waste stream of soybean processing) by a combination of various physico-chemical purification steps.

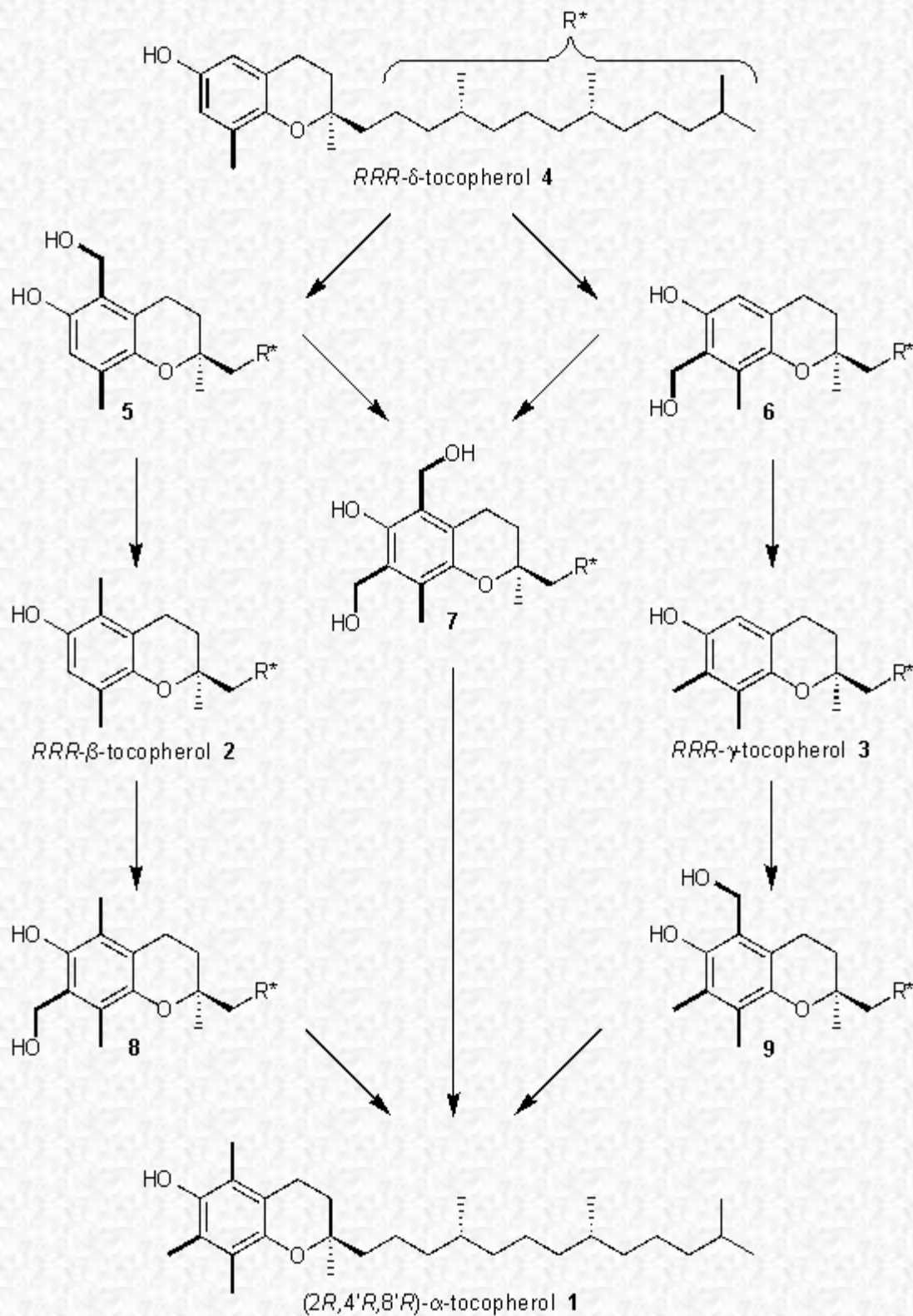
Several methods for the conversion of such mixtures of tocopherols by permethylation to **1** are known, e.g. chloro-, amino-, or hydroxymethylation.¹ In most preferable versions of this transformation the aromatic ring is alkylated with formaldehyde (or an equivalent). Subsequent catalytic reduction yields the permethylated α -tocopherol. A one-pot hydroxymethylation-hydrogenation procedure has been described by a Japanese group, by use of boric acid as a catalyst.² However, serious disadvantages regarding reagents and conditions used limit the value of this process for an industrial application. The process developed in our laboratory (**Scheme 1**) exhibits considerable improvements.



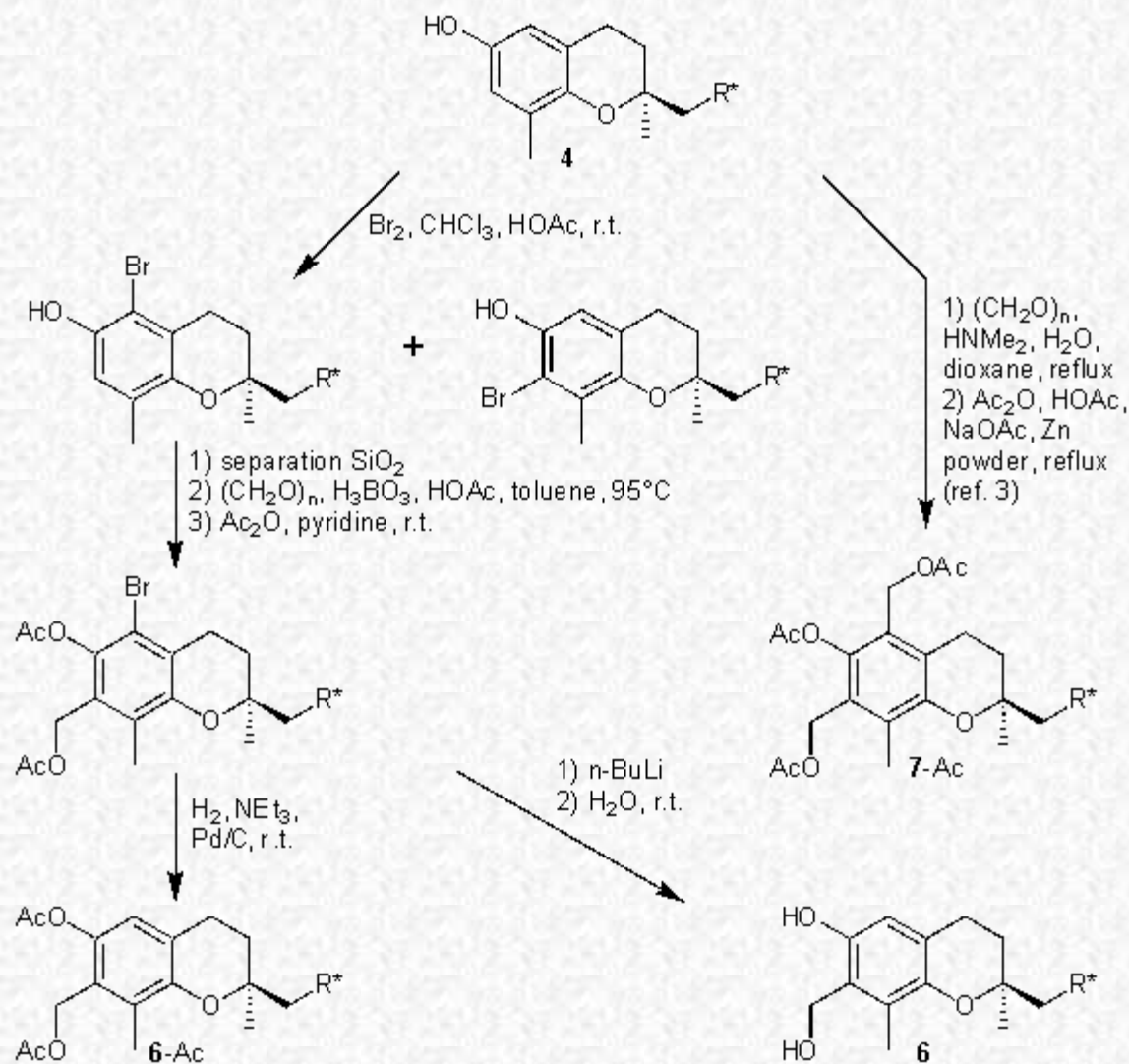
Scheme 1

In order to overcome the difficulties mentioned, we have started a careful investigation of the overall-reaction in detail. We first synthesized all possible hydroxymethyl intermediates (**5-9**, cf. **Scheme 2**), either by known methods (**5**,

8, 9 by hydroxy- or aminomethylation of b-, g-, and d-tocopherol **2-4**, or as depicted in **Scheme 3** (© **6, 7**). Having these reference compounds in hand, mechanistic, kinetic, and analytic studies could be performed which enabled us to fully optimize the reaction parameters. As a result, (2*R*,4'*R*,8'*R*)- α -tocopherol (**1**) can now be prepared by the new process in high yield and stereochemical purity using, surprisingly, less drastic conditions, lower amounts of reactants, and continuous recycling of solvents and boron reagents.

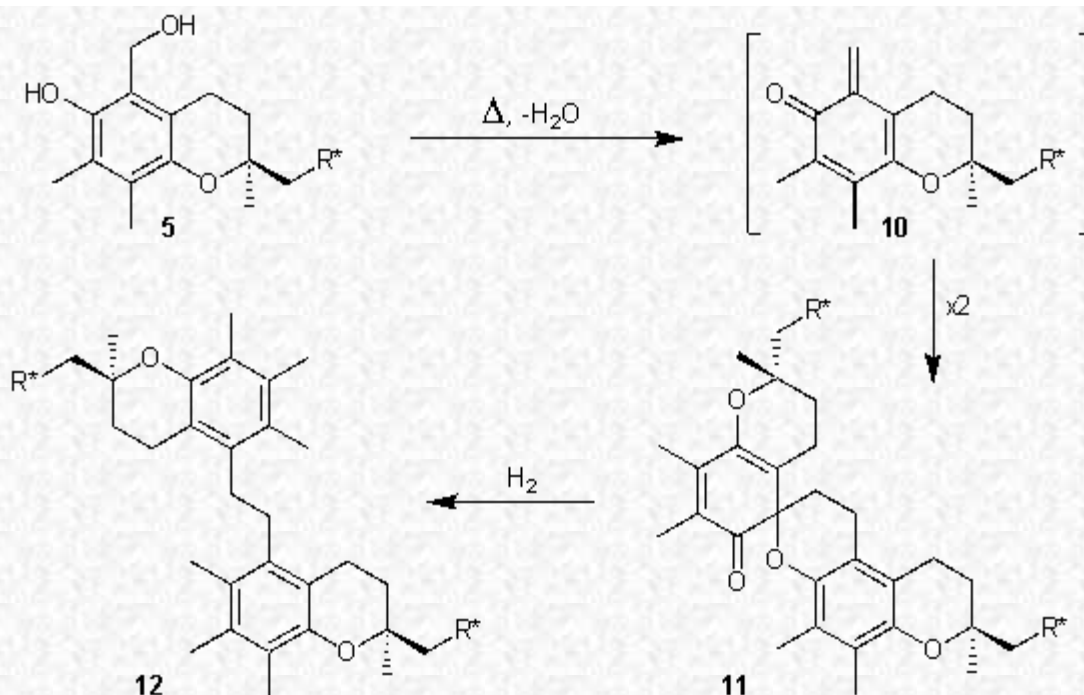


Scheme 2



Scheme 3

Unwanted formation of dimeric by-products as **11/12**, originating from hetero Diels-Alder reaction of o-quinone methide (**10**) formed by thermal dehydration of o-hydroxybenzyl alcohol **5** (Scheme 4) could be avoided under the reaction conditions of hydroxymethylation. The presence of boric acid or trimethyl borate enhances the stability of **5** drastically; 92-97% of starting material could be recovered after 24 h at 100°C , compared to rapid decomposition without boron reagents. It is assumed that this is due to in-situ formation of six-membered cyclic bis-esters derived from boric acid and **5**. The mechanism of dimer formation has been investigated thoroughly.⁴



Scheme 4

The most preferable conditions for the one-pot conversion shown in **Scheme 1** could be realized by heating up starting material (mixture of tocopherols, mainly **3** and **4**) and all reagents in the proper ratio in an autoclave.⁵ Total conversion was obtained under mild reaction conditions (160°C) within several hours. After work-up, acetylation and distillation, stereochemically pure (>99.5% *RRR*) *a*-tocopherol **1** (as its acetate derivative) without detectable amounts of lower homologues (**2-4**) could be isolated in yields of 92-95%. It is remarkable that this is possible in the presence of high proportions of methanol.

Acknowledgement

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References

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