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A novel synthesis of tocopheryl amines and amides

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ABSTRACT

We report the synthesis of tocopheryl amines and amides from commercially available tocopherols. This synthesis improves the yield and diastereomeric purity of these biologically important compounds. The tocopheryl amines were prepared from the corresponding α- and δ-tocopherols using two distinct synthetic routes. The introduction of the C(6)-amino group can be achieved by aryl nitration/reduction or by Pd-catalyzed substitution of an aryl triflate, depending on the structure of the starting material. We also prepared the succinamide and maleamide derivatives of each amine. Tocopheryl amides are more potent pro-apoptotic anti-cancer agents than the corresponding α-tocopheryl esters. These compounds act selectively within the mitochondria of cancer cells.

We and others have been studying synthetic derivatives of vitamin E (VE) with anti-cancer activity, among which α-tocopheryl succinate (**1** in Fig. 1) is the most well known.[1] A remarkable characteristic of this compound is its direct action in the mitochondria, selectively triggering apoptosis in cancer cells.[2] This compound has been shown to induce apoptosis in human breast, prostate, colon, lung, cervical, and endometrial tumor cell cultures, yet it displays virtually no toxicity toward normal non-cancerous cells.[3] Other recent studies have demonstrated similar pro-apoptotic activity toward human neuroblastoma[4] and mesothelioma cells.[5] Considering the low toxicity of α-tocopheryl succinate toward normal cells, its remarkable anti-cancer attributes make it an attractive lead compound for the development of new mitochondrially targeted anti-cancer chemotherapeutic and chemopreventative agents.[6]

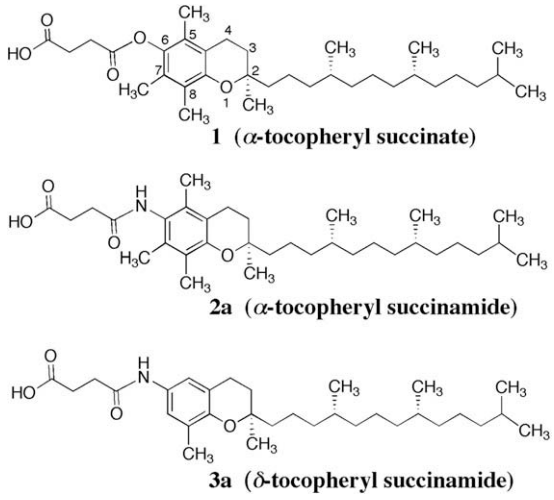

Figure 1. α-Tocopheryl succinate and two representative VE succinamides.

Although there have been extensive in vitro studies on the antitumor activity of VE derivatives, few in vivo studies exist. One obstacle to oral administration is that most tocopheryl esters, including α-tocopheryl succinate, are hydrolytically unstable. These phenolic esters are susceptible to enzymatic cleavage by esterases throughout the body, but mainly within the digestive tract and liver.[7] Thus, tocopherol esters readily undergo hydrolysis in vivo, yielding the free acid and the parent tocopherol. Since α-tocopherol does not induce apoptosis in cancer cells, the hydrolysis of α-tocopheryl esters in vivo poses a limitation to the clinical application of these compounds as anti-cancer agents. The development of VE analogs into more effective chemotherapeutic agents requires that hydrolysis of the drug be minimized, possibly through delivery routes that circumvent intestinal hydrolysis. For example, intravenous administration of tocopheryl esters with new delivery vehicles may enhance clinical efficacy.[8]

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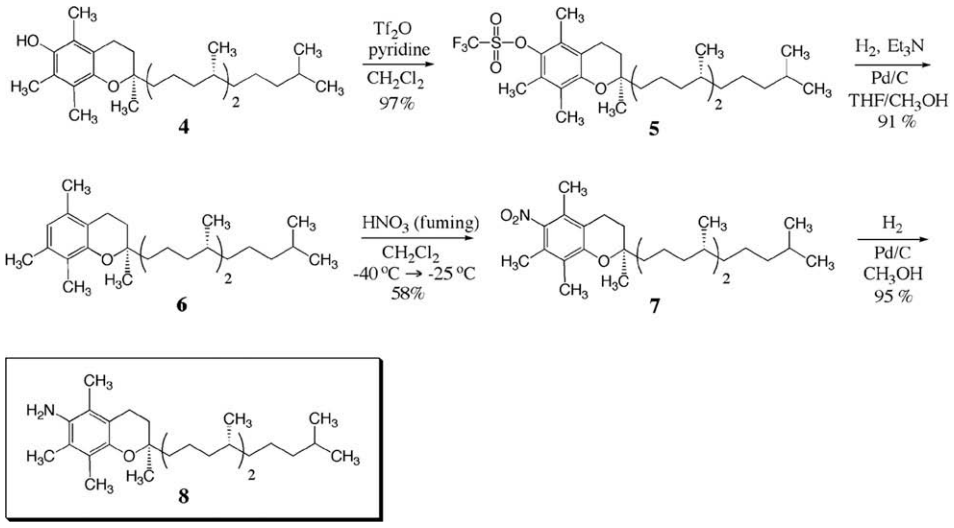


Scheme 1. Synthesis of α-tocopheryl amine from α-tocopherol, using aromatic nitration.

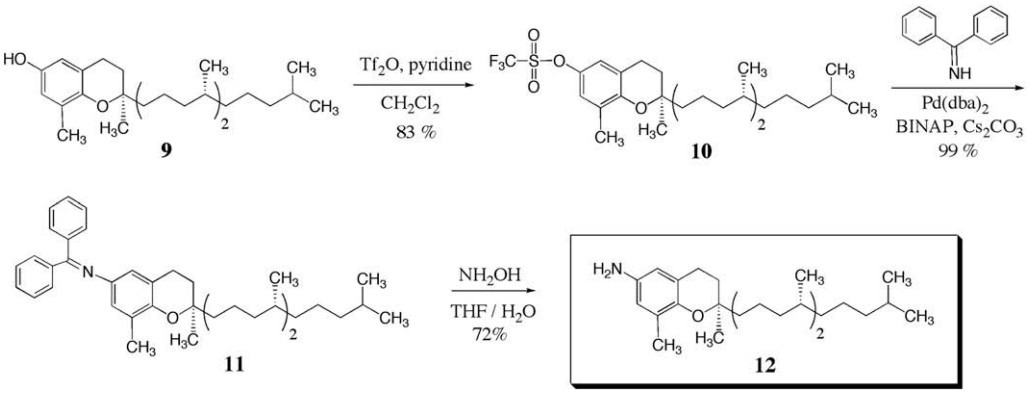
Another approach involves the synthesis of VE analogs that are more resistant to hydrolysis. Some investigators have explored the biological activity of VE ether analogs.[8a,9] The ethers display substantially greater metabolic stability than the esters, since they are not susceptible to esterase-catalyzed hydrolysis. By contrast, we have explored tocopheryl amide analogs, which we reasoned would be more resistant to enzymatic hydrolysis than the parent esters. The structures of the α- and δ-tocopheryl succinamides (**2a** and **3a**) are shown in Fig. 1. The amides are more potent anti-cancer agents in vitro than their ester and ether counterparts, with α-tocopheryl maleamide being the most potent agent tested.[10] We hypothesized that the amide analogs are more rigid than the corresponding ester and ether analogs. Moreover, we expect the amides to have longer in vivo half-lives than the corresponding esters, since peptidase enzymes are far more substrate-specific than esterases. Like tocopheryl esters and ethers, the apoptogenic activity of the VE amides is completely abrogated by esterification of the free carboxyl group.[11]

To date, the only reported method for making amine and amide derivatives of vitamin E is through total synthesis, by combining two smaller molecules [an amino phenol and a large alcohol (phytol)].[12] By today's standards, that synthesis is inefficient, since the overall yield was only 3%, and it produced an inseparable mixture of two diastereomers, epimeric at C(2) of the benzopyran ring.

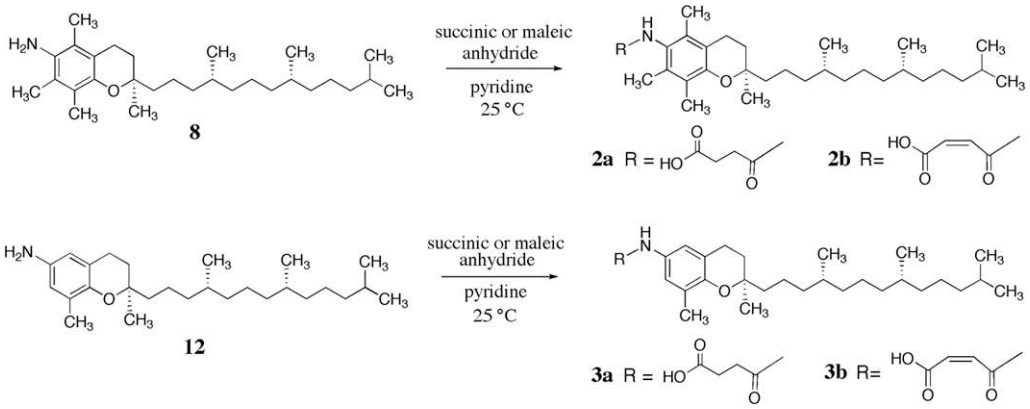
We report a new synthesis of tocopheryl amines and amides. This represents the first new synthesis of tocopheryl amines in over 65 years. We synthesized these amines from commercially available natural tocopherols, rather than through total synthesis. This approach overcomes the problem of diastereomeric product mixtures, and it substantially improves the overall yields. Herein, we demonstrate the syntheses of two VE amines and their amide derivatives, specifically the α- and δ-tocopheryl succinamides, and the α- and δ-tocopheryl maleamides.

The synthesis of α-tocopheryl amine is shown in Scheme 1. It begins with the conversion of α-tocopherol (**4**) to its triflate ester with trifluoromethanesulfonic (triflic) anhydride in pyridine (**5**). This ester was converted to **6** by catalytic hydrogenation with palladium on carbon in the presence of a tertiary amine, which neutralizes the triflic acid generated during this reaction. During the subsequent nitration reaction (fuming nitric acid in CH_2Cl_2, −40 to −20 °C), only a single site on the aromatic ring [C(6) on the benzopyran ring] is open to electrophilic attack by the nitronium ion, providing **7**. However, we also see a small amount of aldehyde formation at one of the aromatic methyl groups (presumably via a *Nef* reaction[13]). Conversion of **7** to α-tocopheryl amine (**8**) was accomplished in good yield with catalytic hydrogenation. Similarly, the reduction of the nitro group in **7** with iron (III) chloride has also been performed with favorable results.

Although the synthetic route shown in Scheme 1 works quite well and represents an advance in the synthesis of α-tocopheryl amine, it is less suitable for the preparation of the three other tocopheryl amines (β, γ, and δ) because multiple aromatic sites are open to nitration in those substrates. Furthermore, this protocol was unsuitable for the synthesis of the tocotrienyl amines series (α, β, γ, and δ), which contain alkenes in their side chains.



Scheme 2. Synthesis of δ-tocopheryl amine from δ-tocopherol, using aryl amination methodology.



Scheme 3. Representative syntheses of tocopheryl amides from the corresponding tocopheryl amines.

To offer wider applicability to the entire series of VE compounds, we developed another synthetic route for the conversion of the other members of the VE family to their corresponding C(6) amines. This route employs Buchwald's palladium-catalyzed *N*-aryl amination chemistry for substituting tocopheryl triflate esters with nitrogen.[14] Scheme 2 illustrates the synthesis of δ-tocopheryl amine (**12**) from δ-tocopherol (**9**). As before, the tocopherol was first converted to the corresponding triflate ester (**10**). However, in this route, the triflate is treated with benzophenone imine and cesium carbonate in the presence of a catalytic amount of palladium *bis*-dibenzylidene acetone [$Pd(dba)_2$] and BINAP (a commonly used bidentate phosphine ligand in aryl amination chemistry) to furnish the corresponding benzophenone imine adduct (**11**).[15] Note that benzophenone imine serves here as an 'ammonia surrogate' to form a new aryl-*N* covalent bond, without promoting dimer or trimer formation. Hydrolysis of **11** was accomplished with hydroxylamine hydrochloride in aq THF to provide the desired δ-tocopheryl amine (**12**). This synthesis provides diastereomerically pure products.[16]

In principle, the chemistry in Scheme 2 can furnish all of the VE amines, but in practice, we found that the synthetic route described in Scheme 1 was still better suited for preparing α-tocopheryl amine, due to the steric hindrance from the two methyl substituents that flank the α-triflate ester.

As anti-oxidants, VE amines are known to be comparable in their reactivity to the parent phenols.[17] Since the tocopheryl amines (**8** and **12**), are unstable in the presence of oxygen, we promptly converted these compounds into the corresponding amides (Scheme 3). The amide formation reactions for each amine (**8**→**2** and **12**→**3**) were run in parallel, employing the appropriate dicarboxylic acid anhydride in pyridine.

Modern aryl amination methodology has never been applied before to members of the VE family. We believe that this research is of interest to the synthetic chemistry community and may facilitate research in areas beyond our own applications.

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Supplementary data

Representative experimental details for the synthesis and the characterization data for key intermediates are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.056.

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