A Vitamin E Derivative as a Novel, Extremely Advantageous Amino-Protecting Group

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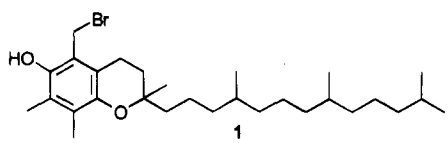
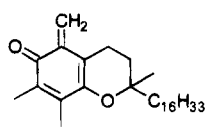
Bromination of α-tocopherol (vitamin E) with elemental bromine produces 5a-bromo-α-tocopherol (**1**)[1] under certain reaction conditions. Reaction of **1** with amines at room temperature and above causes elimination of HBr from **1** producing the *o*-quinone methide **2**, of which two molecules form the spiro-dimer of α-tocopherol (**2a**)[2] in a subsequent hetero-Diels–Alder reaction. In contrast, the reaction of **1** with primary amines at −20 °C leads quantitatively to the corresponding tocopheryl ammonium salt **3**. This chemical behavior renders 5a-bromo-α-tocopherol particularly valuable as an amino-protecting group. This is demonstrated in the following two illustrative examples employing amino-protection: the preparation of secondary amines by alkylation of primary amines, and the synthesis of dipeptides from protected amino acids. The abbreviation "Toc" for the 5a-α-tocopheryl protective group is introduced and used, in addition to other well-established terms, such as Boc or Fmoc. Consistently, **1** is referred to as "Toc-Br".



1



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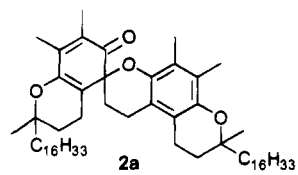
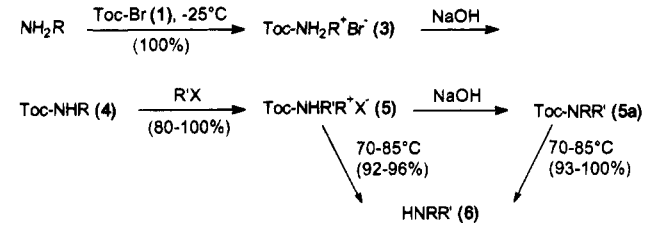


2a

The reaction between alkyl halides and primary amines is not usually a feasible method for the preparation of secondary amines because of the possibility of multiple alkylation, which can lead to the quaternary ammonium salt in the presence of excess alkyl halide. Even with a limited amount of the alkylating agent, the equilibria between the protonated product and the neutral starting amine are sufficiently fast so that a mixture of products is obtained. For this reason, when monoalkylation of an amine is desired, the reaction is usually best carried out by reductive alkylation.[3] The novel reaction sequence illustrated in Scheme 1 employs 5a-bromo-α-tocopherol as the protecting group and leads to secondary amines by alkylation of primary amines in overall yields of 90% and above. Moreover, this reaction sequence overcomes common difficulties encountered in reductive aminations and related reactions.[4] This makes the new approach superior to the reductive alkylation and comparable

Scheme 1



methods not only in yield, but also in the breadth of its applicability and the simplicity of the process.

The primary amine RNH_2 is converted by Toc-Br into the corresponding tocopheryl ammonium bromide **3**.[5] Double alkylation of the amine with **1** as the alkylating agent was not observed, not even if a large excess of Toc-Br was applied. This can be attributed to the bulky shape of the protective group with its C_{16} side chain.[6] After liberation of the tocopheryl-protected amine **4**, alkylation is carried out with a slight excess of alkyl halide R'X.[7] Again, the bulky tocopherol moiety prevents dialkylations, even in the presence of excessive alkyl halide. The products, dialkyl tocopherol ammonium salts **5**, were obtained nearly quantitatively.

While the scope of reaction conditions for introducing the Toc group is limited (−20 °C, aprotic solvents), several ways exist for the removal of the protecting group, resulting in the desired secondary amines **6**. All methods for the removal of the 5a-α-tocopheryl moiety are based on the ready formation of the *o*-quinone methide intermediate **2** upon elimination of the amino "substituent" at position 5a of the tocopherol. This intermediate undergoes consecutive reactions: in aprotic media, the spiro-dimer **2a** is formed quantitatively; in protic media, a mixture of **2a** and α-tocopheryl quinone is obtained. No other byproducts were observed upon removal of the Toc group under the prevailing conditions. In general, removal of the Toc group can be achieved by heating the ammonium salt **5**, or the corresponding dialkyl tocopheryl amine **5a** to 70 °C, either as a pure substance or in a solvent.[8] Other possibilities include the treatment of **5** or **5a** with mild oxidants, preferably Ag_2O, at lower temperatures in organic solvents or with bases

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(1) For preparation and analytical data see: Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51* (29), 7919–7926.

(2) For preparation see: Schudel, P.; Mayer, H.; Metzger, J.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 636–649.

(3) For reviews on reductive alkylation of amines see: Emerson, W. S. *Org. React.* **1948**, *4*, 174–255.

(4) To reduce side reactions during the reductive alkylation of primary amines, an excess of the amine component must be applied. Aliphatic aldehydes with a chain length of up to 6 give extremely low yields. These problems do not occur with the method presented.

(5) A 1 mmol amount of primary amine was dissolved in 50 mL of CH_2Cl_2 (ethyl ether, *n*-hexane, or THF give similar results) and cooled to −25 °C in an inert atmosphere. At the same temperature, a precooled solution of 1 mmol (0.510 g) of **1** in CH_2Cl_2 (25 mL) was added dropwise while stirring. The solution was stirred for an additional 30 min at −20 °C, and the precipitated white solids were removed and washed twice with 10 mL of the solvent applied above.

(6) The reaction of tocopheryl-protected primary amines (Toc-NRH) with excessive Toc-Br (**1**) at room temperature yields Toc-$NRH_2^+Br^-$ and **2a**, besides unreacted starting material. The absence of $Toc_2NRH^+Br^-$ shows that monoalkylations with Toc-Br result from the bulky Toc moiety, but not exclusively from the insolubility of the precipitated ammonium salts.

(7) A 0.1 mol (4.100 g) amount of dry, coarse-grained NaOH was added to a slurry of the obtained ammonium bromide in 50 mL of CH_2Cl_2, and the mixture was stirred vigorously for 10 min at −20 °C under exclusion of oxygen. The solids were carefully removed. To the solution of the N-protected amine obtained, 1.1 mmol of alkyl halide was added dropwise at room temperature. The solution was stirred for about 30 min. The dialkyl tocopheryl ammonium salt, obtained as a white solid, was removed, washed thoroughly with a total of 20 mL of CH_2Cl_2, and dried under vacuum.

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Table 1. Secondary Amines by Alkylation of *N*-Toc Protected Primary Amines, Followed by Removal of the Toc Group

product	overall yield, %
N-butylethylamine	95
N-allylcyclopentylamine	90
di-*n*-octylamine	98
diallylamine	85
N-ethylnaphthylamine	84
N-benzylmethylamine	92
N-ethylalanine	96
N-benzylleucine	92
2-(methylamino)isobutyric acid	98
2-(benzylamino)glutamic acid	93

in aqueous media.[9] Hence, several methods to remove the amino-protecting group are available, so that the choice can adapt to the needs for special reaction conditions set by the respective amines or other protecting groups employed. In all cases, the hydrophilicity of the secondary amines produced can be utilized to separate them in extraction processes from the strongly hydrophobic products of the cleaved protecting group. The separation of the secondary amines as the corresponding ammonium salts is an even more convenient procedure.

5a-Bromo-α-tocopherol proved to be a valuable reagent for the protection of amino functions in amino acids.[10] In fact, the reaction of **1** with the amino group of amino acids can be interpreted as a special case of the above-described procedure, since amino acids with unsubstituted NH_2 groups can be regarded as primary amines. The corresponding *N*-Toc amino acids are prepared in the same fashion as the tocopheryl protected primary amines, giving also quantitative yields.[11] N-Alkylation of the *N*-Toc amino acids with alkyl halides, followed by the removal of the amino-protecting group, results in high yields of *N*-alkyl amino acids. This procedure resembles the sequence presented in Scheme 1.

N-Alkylation of amino acids is less common in synthetic organic chemistry than the coupling of amino acids to di- or oligopeptides. Toc-Br as an amino-protecting group also shows promising behavior in this field. Encouraging preliminary results were obtained from the synthesis of dipeptides **9** according to the DCC-method,[12] employing amino acids **7** that had been protected by **1**. The reaction sequence is shown in Scheme 2; products and yields are listed in Table 2.[13] The overall yield of the reaction sequence is determined exclusively by the coupling reaction between the *N*-Toc-protected and the carboxyl-protected amino acid, since both installation

Scheme 2

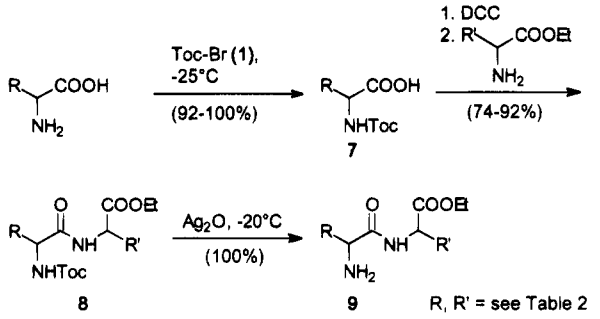

Table 2. Dipeptides by DCC-Coupling of *N*-Toc Protected Amino Acids and Amino Acid Ethyl Esters, Followed by Removal of the Amino-Protecting Group

product	*N*-Toc protected amino acid	overall yield, %
Ala-Ala	*N*-Toc-Ala	96
Ala-Cys	*N*-Toc-Ala	90
Cys-Cys	*N*-Toc-Cys	68
Gly-Gly	*N*-Toc-Gly	92
Leu-Ala	*N*-Toc-Leu	93
Leu-Leu	*N*-Toc-Leu	93

and removal of the protecting group from the *N*-Toc protected dipeptide **8** are quantitative or nearly-quantitative steps.[14]

The Toc group is stable to a wide range of reaction and workup conditions: it is inert to mild or even harsh acidic conditions, Lewis acids, and hydrogenations and is also stable to mild bases, e.g., commonly applied basic auxiliaries, such as DBU or *N*-ethyldiisopropylamine. In addition, the conditions required for the removal of the Toc protecting group are selective and mild enough to tolerate the widest range of complementary protecting groups. Therefore, it might well serve in different orthogonal sets of protecting groups.[15]

Further work is now aimed at obtaining generalizations of the method and determining the full scope of the reaction in the chemistry of amino acids and peptides. Nevertheless, the results obtained so far justify the ranking of 5a-bromo-α-tocopherol among the most valuable amino-protecting groups. Since it even proves to be superior to those groups in several aspects, it will certainly find broad applicability and is expected to become a useful tool in amine and amino acid chemistry.

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Supporting Information Available: Synthetic procedure and analytical and NMR data of products and two representative examples of *N*-Toc-protected primary amines (10 pages).

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(8) The ammonium salts obtained according to ref 7 were warmed to 70 °C for 1 h or to 85 °C for 10 min. The heat treatment is carried out under exclusion of oxygen, either as a pure substance or as a suspension of the salt in dry aprotic solvents, preferably toluene or dioxane.

(9) Probably the mildest and most widely applicable procedure for the removal of the 5a-tocopheryl group is its oxidative cleavage. For this purpose, the dialkyl tocopheryl ammonium salts are suspended in *n*-hexane or dichloromethane (50 mL) and stirred with 2 mmol freshly prepared Ag_2O for 30 min at −20 °C. $AgNO_3$ or AgBr can also be used instead of Ag_2O.

(10) A thorough survey of protective groups, especially the protection of amino functions in amino acids, is given by: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd ed.; Wiley: New York, 1991, and references cited therein.

(11) The statement about quantitative yields must be restricted to amino acids or other compounds with only one primary amino function.

(12) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis*, 2nd rev. ed.; Springer Verlag: Berlin, New York, 1994.

(13) The reactions presented in Scheme 2 were also carried out using *O*-methyl-5a-bromo-α-tocopherol.

(14) The same experimental procedure as described for primary amines (see refs 5, 7−9) applies to introduction and removal of the Toc group in the amino acid chemistry.

(15) Numerous common protecting groups, e.g., Bn, Boc, Z, and Fmoc, are normally installed using their halide derivatives in the presence of auxiliary bases. The Toc group proved to be stable under these conditions. On the other hand, the very mild conditions used to attach Toc-Br to amines do not impair any of those groups. Removal of protecting groups under acidic conditions (e.g., Boc, Z), with Lewis acids (e.g., Boc) or by hydrogenolysis (e.g., Bn, Z, Fmoc) do not interfere with tocopheryl-protected structures present. Basic conditions for the cleavage of a protecting group (e.g., Fmoc) are only safe as long as mild bases in aprotic media are used (e.g., pyridine, triethylamine in DMF). Strong bases in aqueous media, however, lead to deprotonation and immediate cleavage of the Toc group.