

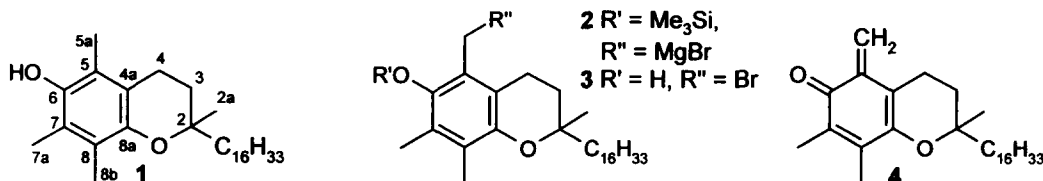
Novel Tocopherol Compounds - X. A Facile Synthesis of *O*-Trimethylsilyl-5a-halo- α -tocopherols

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Abstract: A simple and efficient procedure for the synthesis of *O*-trimethylsilyl-5a-bromo- α -tocopherol (**6**) and *O*-trimethylsilyl-5a-chloro- α -tocopherol (**7**) starting from *para*-tocopherolquinone (**5**) has been developed. The products are formed by acid-catalyzed cyclization of *para*-tocopherolquinone via an *ortho*-quinone methide intermediate. © 1997 Elsevier Science Ltd.

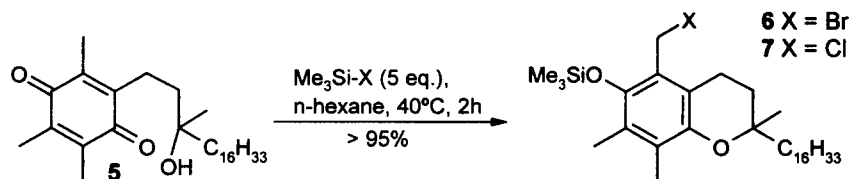
Within the past several years, 5a-substituted tocopherols have attracted considerable interest as auxiliaries in synthesis,¹ enzyme inhibitors,² and possible drug carriers derived from vitamin E (**1**). The reaction of „ α -tocopheryl-Grignard” (**2**) with carbonyl compounds³ is the most general approach to substituted tocopherols with the tocopheryl moiety being tightly bound to another structure by a stable carbon-carbon bond extending from C-5a. So far, the only way to generate this organomagnesium derivative of vitamin E comprises the synthesis of 5a-bromo- α -tocopherol (**3**) followed by protection of the phenolic OH group as trimethylsilyl ether, and reaction with magnesium metal. Although providing good yields, the procedure has some drawbacks: 5a-bromo- α -tocopherol (**3**) is a labile compound that cannot be stored and must be newly prepared each time before use. In addition, extended reaction times are required for the OH-protection since basic auxiliaries have to be avoided in this process due to the sensitivity of **3** towards bases.



Surprisingly, silylation of 5a-bromo- α -tocopherol (**3**) containing *para*-tocopherolquinone (**5**) as an impurity afforded *O*-trimethylsilyl-5a-bromo- α -tocopherol (**6**) as the only product, meaning that both **3** and **5** yield **6** upon treatment with trimethylsilyl bromide. Resulting from this observation, the possibility of obtaining pure **6** starting from *para*-tocopherolquinone (**5**) was further examined. The reaction of **5** with three equivalents of trimethylsilyl bromide leads to a complete conversion into *O*-trimethylsilyl-5a-bromo- α -tocopherol (**6**) within 72 h. The reaction time can be shortened to 2h by using a fivefold amount of silylating agent and working at 40°C.⁴

The mechanism of the process comprises two steps, namely the acid-promoted dehydrative cyclization of *para*-tocopherolquinone (**5**) leading to a transient *ortho*-quinone methide **4**, and subsequent addition of the trimethylsilyl halide to this intermediate. This addition reaction seems to be the preferred process since products resulting from the dimerization of two molecules of the *ortho*-quinone methide **4** were not formed at all. The

formation of **6** or **7** is completely suppressed in the presence of a basic auxiliary, for example pyridine, which accounts for the acid-catalysis of the reaction. Moreover, the intermediacy of the *ortho*-quinone methide **4** could be shown by a trapping reaction with ethylvinyl ether. Resulting from this mechanism and also in accordance with experimental results, three equivalents of trimethylsilyl halide are the minimum requirement to achieve complete conversion of **5**: one equivalent remains in the product, while the two others are consumed by water formed in the cyclization process. The reaction shows similarities to the addition of acetyl chloride to *para*-tocopherolquinone (**5**).⁵ Although reaction of **5** with Me₃SiBr or Me₃SiCl provided highest yields, addition of trimethylsilyl iodide or trimethylsilyl cyanide in an analogous procedure was not viable: a complex mixture of products was obtained when Me₃SiI was used, whereas no reaction was observed with Me₃SiCN.



The new route to *O*-trimethylsilyl-5a-halo- α -tocopherols **6** and **7** employs *para*-tocopherolquinone (**5**) as the starting material, a common oxidation product of vitamin E that is stable, storable, and available in gram amounts. The procedure is extremely convenient and, thus, superior to the method used so far.

ACKNOWLEDGEMENT

The financial support by the Studienstiftung des Deutschen Volkes (doctoral fellowship to T.R.) and by the DFG (Graduiertenkolleg "Structure-Property Relationships in Heterocycles") is gratefully acknowledged.

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- General procedure*: ¹H NMR spectra were recorded at 300 MHz, ¹³C NMR spectra at 75 MHz on a Bruker AC-300P. The δ -values of the atoms of the isoprenoid side chain (C-1' to C-13') are well established and will not be listed in the following since they are only very slightly affected by modifications of the chroman structure.

O-trimethylsilyl-5a-bromo- α -tocopherol (**6**). In an inert atmosphere, a solution of **5** (3.00 mmol, 1.338 g) and Me₃SiBr (15.00 mmol, 1.875 g) in 10 mL of dry n-hexane was stirred for 2 h at 40 °C. Solvent and excess of silylating agent were removed under reduced pressure. The oily residue was dissolved in 10 mL of diethyl ether and passed through a layer of anhydrous aluminum oxide. The resulting filtrate contained pure **6**. Anal. Calcd. for C₃₂H₅₇O₂BrSi: C, 66.06; H, 9.87; Br, 13.73. Found: C, 66.12; H, 9.74; Br, 13.94%. ¹H NMR (CDCl₃): δ 0.08 (9H, s, Si(CH₃)₃), 1.73 (2H, m, ³CH₂), 2.04; 2.07 (2 x 3H, 2 x s, ^{7a}CH₃ and ^{8b}CH₃), 2.69 (2H, t, ⁴CH₂), 4.57 (2H, s, ^{3a}CH₂Br). ¹³C NMR: δ 1.9 (Si(CH₃)₃), 12.1 (^{8b}C), 12.2 (^{7a}C), 19.2 (⁴C), 23.7 (^{2a}C), 27.5 (^{5a}C), 31.0 (³C), 74.9 (²C), 117.4; 119.4; 122.3; 127.1; 145.5; 146.0 (^{4a}C).

O-trimethylsilyl-5a-chloro- α -tocopherol (**7**). The compound was prepared according to the procedure described for the synthesis of **6** with Me₃SiCl instead of Me₃SiBr. Anal. Calcd. for C₃₂H₅₇O₂ClSi: C, 71.53; H, 10.69; Cl, 6.60. Found: C, 71.66; H, 10.84; Cl, 6.83%. ¹H NMR (CDCl₃): δ 0.08 (9H, s, Si(CH₃)₃), 1.75 (2H, m, ³CH₂), 2.10; 2.12 (6H, 2 x s, ^{7a}CH₃; ^{8b}CH₃), 2.65 (2H, t, ⁴CH₂), 4.78 (2H, s, ^{3a}CH₂Cl).

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(Received in Germany 12 May 1997; accepted 26 June 1997)