SYNTHESIS OF BIS(TRIFLUOROMETHYL)CHROMANOLS

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Dedicated with admiration and respect to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Abstract - Dimethylhydroquinones (**1a-c**) were treated with 6-chloro-3-methyl-2-hexen-1-ol in the presence of zinc chloride to give 2-(3-chloropropyl)chromanol derivatives (**2a-c**), which were methoxymethylated and condensed with trifluoroacetone through the corresponding phosphonium salts (**4a-c**) to 5,5,5-trifluoro-4-methyl-3-pentenylchromanols (**5a-c**). 2,5,7-Trimethyl compound (**5a**) was iodinated and treated with trifluoromethyl iodide and copper powder followed by deprotection and hydrogenation to give 4',8-bis(trifluoromethyl) compound (**9a**). 4',5-And 4',7-bis(trifluoromethyl) compounds (**9b** and **9c**) were derived from **5b** and **5c** through bromine compounds.

Vitamin E was found about 70 years ago as an antisterility vitamin, and named "tocopherol." Since then, its function has been investigated widely and now its activity is believed due to antioxidant agent of unsaturated fatty acids that constitute important biological membranes.[1] It is suggested that vitamin E is deeply related to aging,[1] too. However, its mechanism of action is still not clear. We have already synthesized fluorine analogs of vitamin E, where one of the methyl groups is substituted with a trifluoromethyl group.[2,3] Their behaviors in liposome were

investigated by measuring spin-spin relaxation times (T_2) on fluorine nmr. This study told us how and where these vitamin E derivatives were incorporated in the liposome, a model of biological membranes.[4] As the extension of this study, we planned synthesis of fluorine analogs of vitamin E in which its two methyl groups were replaced with two trifluoromethyl groups, one on the chromanol ring and the other on the isoprenoid side chain. More detailed study using these compounds would help understanding the function of vitamin E. We applied our previous reactions[2,3] to this synthesis. However, we encountered some difficulties during the syntheses. Therefore, we carried out some model experiments. Here, we would like to report these experiments preliminarily.

Previously, we reported that 2-(3-chloropropyl)chromanol derivatives (**2**) were useful intermediates for synthesis of tocopherols having various side chains, containing a trifluoromethyl group.[2] Compounds (**2a-c**) were synthesized by the reaction of the corresponding hydroquinones (**1a-c**) with 6-chloro-3-methyl-2-hexen-1-ol in the presence of zinc chloride.[5] Compounds (**2a-c**) were methoxymethylated and converted to phosphonium salts (**4a-c**), which were treated with butyllithium, potassium tertiary butoxide and trifluoroacetone to give chromanol derivatives (**5a-c**) having a short side chain with a trifluoromethyl group. These results are shown in Scheme 1 and the yields of the all steps are summarized in Table 1. All the reactions proceeded as expected from our previous results, and this suggested that this strategy could be used for the introduction of a longer trifluoromethylated side chain than that of **5**.

We reported previously the introduction of a trifluoromethyl group to the chromanol moiety,

Scheme 1

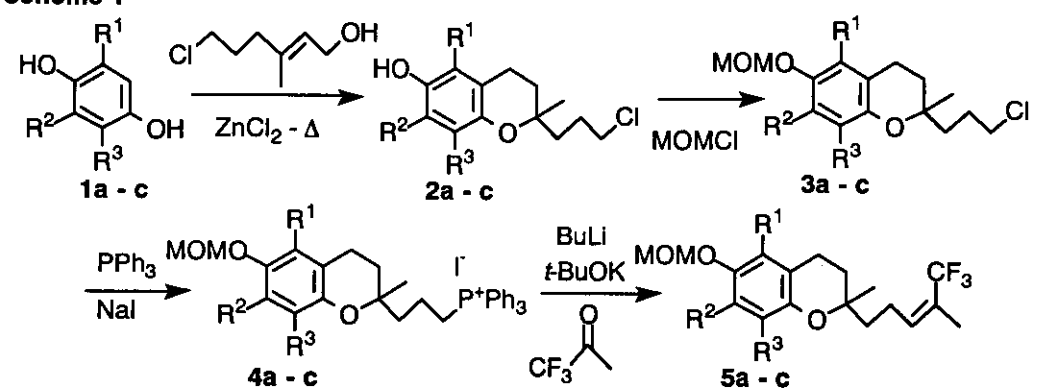
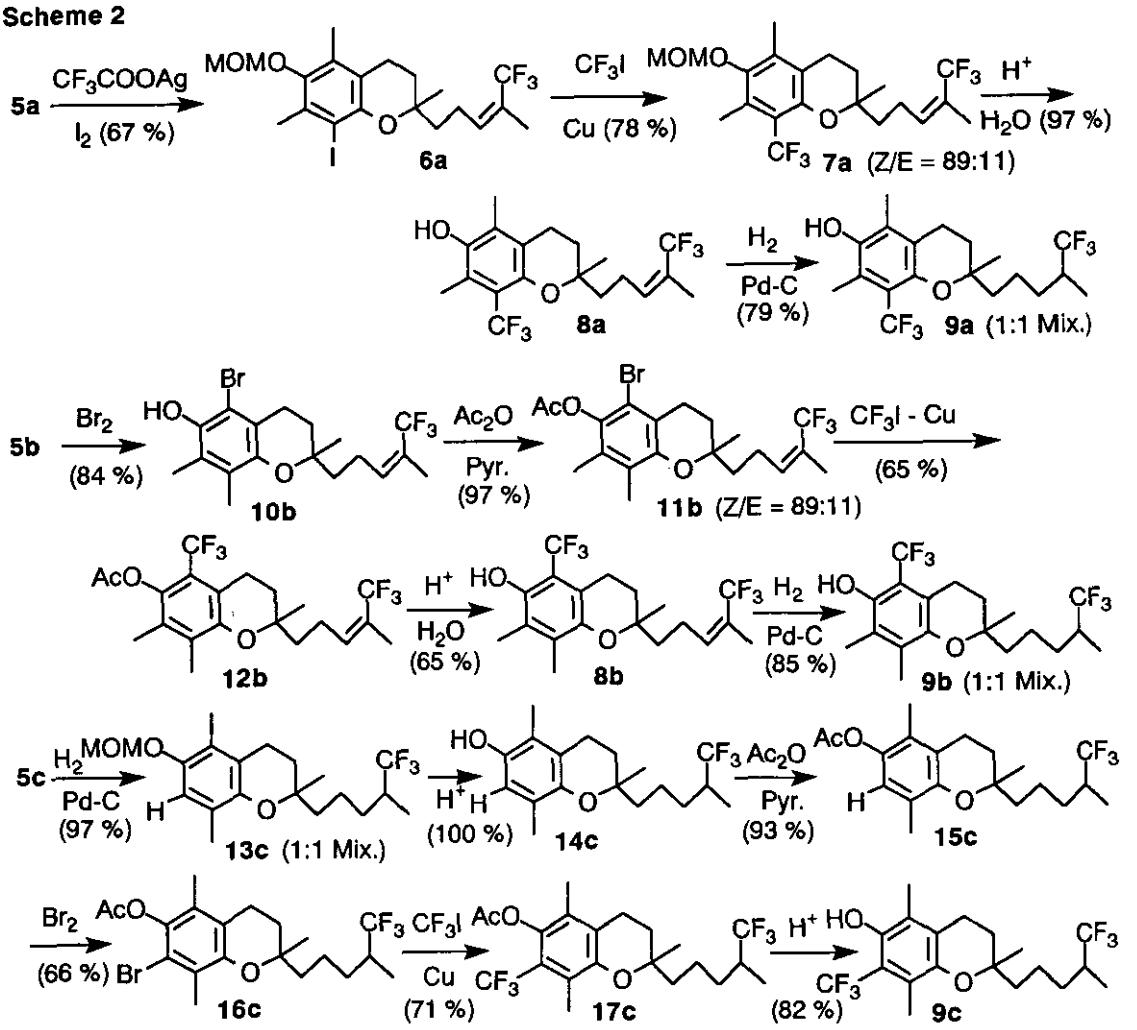


Table 1 . Yields of **2** to **5**.

	R^1	R^2	R^3	2	3	4	5
a	Me	Me	H	71 %	90 %	87 %	84 %
b	H	Me	Me	61 %	90 %	92 %	88 %
c	Me	H	Me	50 %	92 %	92 %	83 %

which was iodination of a chromanol compound in the presence of silver trifluoroacetate and subsequent treatment with trifluoromethyl iodide and copper powder.[3] Application of this

Scheme 2



method to **5a** gave the bis(trifluoromethyl) compound (**7a**), as expected. This compound was hydrolyzed and hydrogenated in the presence of palladium-carbon to give bis(trifluoromethyl)chromanol compound (**9a**). However, the iodination of **5b** resulted in the formation of a bis(chromanol) compound, probably through an oxidative dimerization of a phenol derivative. To avoid this oxidation, **5b** was brominated first. During this bromination, the methoxymethyl group was hydrolyzed to afford bromochromanol (**10b**). This chromanol was acetylated and treated with trifluoromethyl iodide and copper powder to give 8-trifluoromethyl compound (**12b**), which was hydrolyzed and hydrogenated to **9b**. The iodination of **5c** resulted in the iodination of the double bond on the side-chain and phenolic oxidation. Therefore, the double bond was hydrogenated first and the protective group was changed to an acetyl group then brominated to bromo acetate (**16c**),which was trifluoromethylated as above and hydrolyzed to 7-trifluoromethyl compound (**9c**). These results are summarized in Scheme 2.

In conclusion, the halogenation of the chromanol moiety of tocopherol was found to be a key step for the synthesis of bis(trifluoromethyl)chromanol compounds. These results will help the synthesis of bis(trifluoromethyl) analogs of vitamin E.

REFERENCES AND NOTES

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3) I. Kumadaki, M. Hirai, M. Koyama, T. Nagai, A. Ando, and T. Miki, *Synth. Commun.*, 1989, **19**, 173.

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5) The structures of new compounds were determined by spectral data including high resolution mass spectra and ^{19}F-nmr.

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