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PREPARATION OF 2-TRIFLUOROMETHYLVITAMIN K ANALOGS

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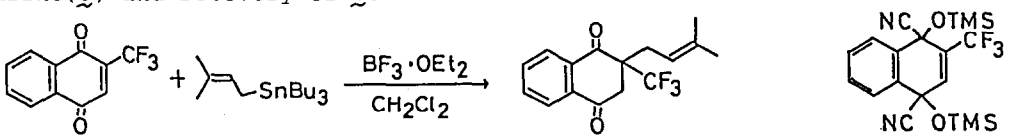
Summary: 2-Trifluoromethylvitamin K analogs(6) were efficiently prepared through allylation of the MOM ether(4) followed by oxidation.

Presently available data on vitamin K-dependent and O_2-dependent carboxylation of glutamyl(Glu) residue to yield γ-carboxyglutamyl(Gla) residue in protein, prothrombin and clotting factors, indicates the vitamin K-dependent deprotonation at the γ-position of the Glu residue in a reaction to possibly occur in conjunction with the formation of vitamin K-2,3-epoxide.[1] However, it is still unclear how to couple these reactions and whether carboxylation couples to the formation of the 2,3-epoxide. Moreover, the structure and chemical property of the proposed oxygenated intermediate formed from reduced vitamin K and molecular oxygen remain to be clarified. Vitamin K analog having 2-trifluoromethyl instead of 2-methyl would be a useful tool to clarify these points, since the incorporation of fluorine may bring about appreciable change in electronic state, but little in steric alteration, and high susceptibility of fluorine in nmr makes it possible to follow a successive process by nmr. Herein, we report an efficient preparation of 2-trifluoromethylvitamin K analogs(6) through selective deprotonatin at the 3 position of 4.

We reported a synthesis of 2-trifluoromethylnaphthoquinone(1) through the Diels-Alder reaction of 1-phenylsulfonyl-3,3,3-trifluoropropene.[2] Further elaboration of introduction of allylic substituent into the 3 position of 1 was made according to the several methods successfully applied to 2-methylnaphtoquinone,[3-5] but failed. For example, Lewis acid catalized allylation of 1 with prenylstannane[3] afforded 2-prenyl-2-methyl-2,3-dihydro compound(2), while reaction of 1 with TMSCN[4] resulted in the formation of 1,4-biscyanohydrine(3) and recovery of 1.

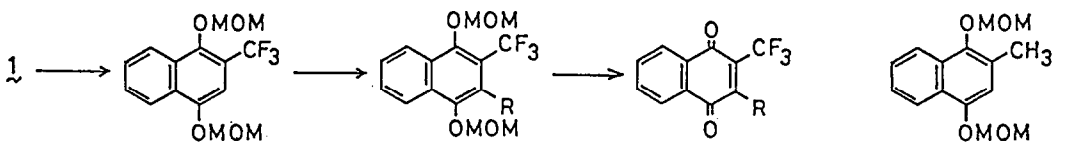


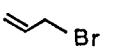
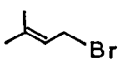
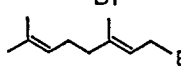
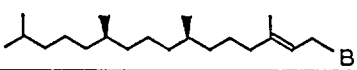
1 2 3

We found that the presence of the trifluoromethyl group facilitates the selective deprotonation at the 3 position of the MOM ether(4) (n-BuLi, THF, -40°C, 20 min)[6,7] confirmed by quantitative deuteration with D_2O, while with 2-methyl derivative(7) slow reaction (n-BuLi, THF, rt, 2 h) and competitive

deprotonation (C-3 vs CH_3) were observed.[8)]

The MOM ether(4) was obtained in 87% yield by treatment of 1 with Zn (THF-AcOH, rt, 5 min) followed by methoxymethylation (MOMCl-iPr_2NEt, THF, rt, 12 h). Allylation of 4 was carried out by treating the lithiated compound formed as above with an allylic bromide R-Br in the presence of CuBr·Me_2S (THF, -78°C, 1-2 h) to give the 3-substituted product(5) in 42-72% yield. The desired trifluorovitamin K analogs(6) were obtained by removal of MOM group of 5 (10% HCl-THF-iPrOH, rt) followed by MnO_2 oxidation (CH_2Cl_2, rt) or Ce(IV) oxidation of 5d [$(NH_4)_2Ce(NO_3)_6$, CH_3CN-H_2O, rt, 20 min)].



Run	R-Br	4→5	Yield (%)		5→6	Yield (%)
1		5a	72	1) H_3O^+ 2) MnO_2	6a	32
2		5b	52	"	6b	51
3		5c	42 a)	"	6c	45
4		5d	58	Ce(IV)/CH_3CN	6d	83 b)

a) CuI was used in place of CuBr·Me_2S. b) Z-isomer of 6d formed in the oxidation step was also isolated in 7% yield.

References and Notes

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9) A study on the activity of the trifluoro analogs(6) as the substrate and inhibitor of vitamin K-dependent carboxylase has been carried out by Prof. J. W. Suttie(Wisconsin Univ.). The results will be reported elsewhere.

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