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REGIO- AND STEREOCONTROLLED POLYPRENYLATION OF QUINONES.[1] A NEW SYNTHETIC METHOD OF VITAMIN K SERIES

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Polyprenyltrimethyltins were prepared in high yields by the coupling reaction of polyprenyl halides (geranyl, nenyl, farnesyl, and phytyl chloride) with trimethyltinlithium with retention of the stereochemistry at Δ^2 position. In the presence of $BF_3{\cdot}OEt_2$, coupling of the resulting polyprenyltin reagents with 2-methyl-1,4-naphthoquinone occurred to give vitamin K_1 and K_2 without any loss of their stereochemistry in the prenyl side chain.

Introduction of an isoprenyl functionality into a quinonoid nucleus is of vital interest in view of synthesis of naturally occurring and/or physiologically active quinones.[2] In most cases the site of functionalization and the stereochemical fate of the introduced moiety are of paramount importance; the trans configuration of isoprenyl side chain in the naturally occurring quinones is requisite. Only a few example,[3] however, are known about the regio- and stereoselective polyprenylation of protected quinones with use of the well-known coupling reactions. A limited number of direct polyprenylation[4] has been reported, but the yields are not satisfactory contaminated with undesirable side products.

Recently we established the direct allylation of quinones in a fair yield with use of allyltributyltin.[5] We wish to report the stereoselective synthesis of polyprenyltin reagents and the new regio- and stereocontrolled synthesis of vitamin K series. These quinones are involved in normal blood clooting and oxidative phosphorylation.

We newly prepared four polyprenyltin compounds 2a~d by coupling of corresponding polyprenyl chlorides 1a~d with trimethyltinlithium. (Scheme 1) The following procedure for the preparation of geranyltrimethyltin is representative of the stannylation. To the THF solution (40ml) of trimethyltinlithium (0.04mol) geranyl

chloride (7.4g, 0.043mol) in THF (10ml) was added under nitrogen atmosphere at -60°C, then after 1h the reaction mixture was quenched by the addition of aqueous saturated ammonium chloride solution at -20°C. After extraction with ether organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give geranyltrimethyltin 2a (9.0g, 0.03mol); bp 105-107°C/1mm. ^{1}H-NMR($CDCl_3$); δ0.08(s, 9H, $Sn(CH_3)_3$, $J_{Sn^{117}-H}$= 51Hz, $J_{Sn^{119}-H}$=55Hz), 1.56(s, 3H, *trans*-CH_3 nearest Sn), 1.62(s, 3H, terminal *trans*-CH_3), 1.66(s, 5H, terminal *cis*-CH_3 and $SnCH_2$), 1.97(m, 4H, CH_2CH_2), 5.00(bs, 1H, CH=C), 5.24(t, 1H, CH=C, J=8Hz), IR(neat); 2960(vs), 2900(vs), 2840(sh), 1645(w), 1440(m), 1375(m),1115(m), 755cm^{-1}(m). Anal. ($C_{13}H_{26}Sn$) C, H.[7] The stereochemistry at Δ^2 position was determined to be *trans*:*cis*=95:5 by GLPC analysis. The coupling reaction proceeded S_N2 type reaction with perfect retention of the stereochemistry at Δ^2 position in a fair yield without any allylic rearrangement. The other polyprenyltin reagents were prepared similarly. (Table 1)

Synthesis of vitamin K_1 (4d) was undertaken by coupling 2-methyl-1,4-naphthoquinone (3) with phytyltrimethyltin (2d) as follows. To a dichloromethane solution (20ml) of 3 (172mg, 1.0mmol) BF_3OEt_2 (3.0mmol) was added under N_2 at -78°C. After that phytyltrimethyltin (532mg, 1.2mmol) was added, and the temperature of the re-

Scheme 1.

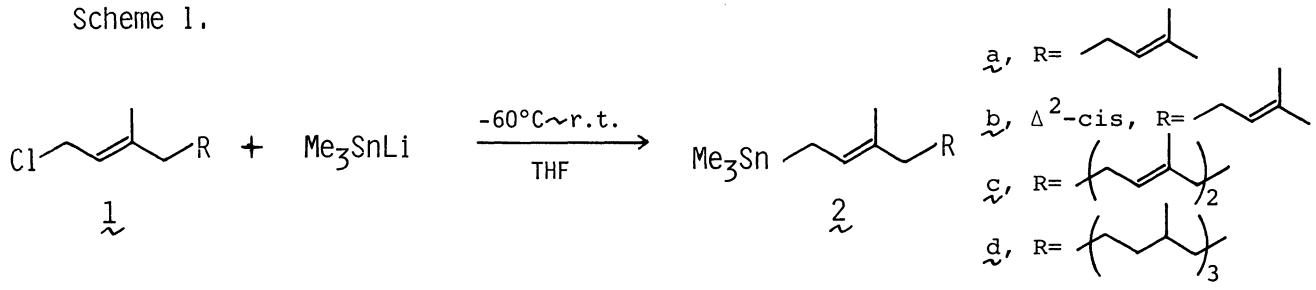


Table 1. Synthesis of Polyprenyltrimethyltin (2a~d)

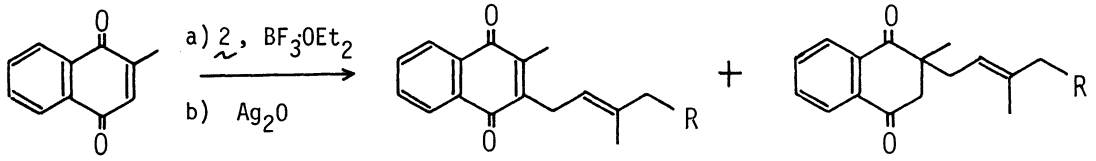
	Polyprenylchloride 1 Stereochemistry at Δ^2, *trans/cis*[a]	Polyprenyltin 2 Yield,%	Stereochmistry at Δ^2, *trans/cis*
a	95/ 5	70[c]	95/ 5[b]
b	5/95	69[c]	4/96[b]
c	~60/40	quant.[d]	~60/40[a]
d	100/ 0	quant.[d]	100/ 0[a]

[a] Determined by ^{1}H-NMR. [b] Determined by GLPC. [c] Isolated yield after purification by distillation. [d] Isolated yield after purification by short path column chromatography.

sulting solution was gradually elevated to -65°C within 1h. Then, ether and aqueous saturated NaCl solution were added to the reaction mixture. The organic layer and the combined ether extract were dried over anhydrous magnesium sulfate. Subsequent oxidation with excess silver oxide gave crude vitamin K_1 after solvent was evaporated *in vacuo*. The resulting crude product was purified by preparative TLC on silica gel; affording 4d (176mg) and 5d (39mg). The ^{1}H-NMR of 4d showed one singlet at δ 1.78ppm, assignable to be trans olefinic methyl group of C-3'. Moreover, by medium pressure LC the isomeric ratio was accurately determined to be *trans*:*cis*=96:4. Thus, vitamin K_1 was directly prepared with complete retention of stereochemistry. The above method was extended to other polyprenyltin reagent (2a~c) to give vitamin $K_{2(m)}$ (m=10, 15) (4a~c) without any loss of trans stereochemistry. (Table 2.)

To obtain a higher conversion and a higher regioselectivity, use of other stronger Lewis acid,[6] i.e. $TiCl_4$, $SnCl_4$, was examined, but resulted in vain so far yielding only hydroquinone and/or quinhydron of the starting quinone. Optimum reaction conditions are now under investigation.

Scheme 2.



3 4g~d 5g~d

Table 2. Coupling Reactions to Yield Vitamin K_1 and K_2[a]

	Yield, %[b] 4	5	4, Stereochmistry at Δ^2, trans/cis
a	46(100)	trace	95/ 5
b	41(73)	trace	24/76
c	25(45)	18(23)[c]	79/21
d	48(70)	14(17)[c]	96/ 4

[a] Fully characterized by spectroscopic methods and elemental analysis. [b] The yield based on a consideration of the amount of the starting quinone recovered is shown in parentheses; all others are determined by ^{1}H-NMR. [c] Stereochemistry at Δ^2 position is not determined.

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References and Notes

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6) The complexation to carbonyl is stronger than BF_3OEt_2; B.P.Susz, Bull. Soc. Chim. Fr., 2671 (1965). The role of Lewis acid in the allylation of quinone with allyltin reagents has been already established by the present authors; activation of carbonyl group of quinone and catalytic effect to dienone-phenol rearrangement.

7) Found; C, 51.87; H, 8.71%. Calcd for $C_{13}H_{26}Sn$; C, 52.03; H, 8.63%.

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