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REGIO- AND STEREOCONTROLLED POLYPRENYLATION OF QUINONES.[1] A NEW SYNTHETIC METHOD OF COENZYME Q_2, Q_3, Q_9, AND Q_{10}

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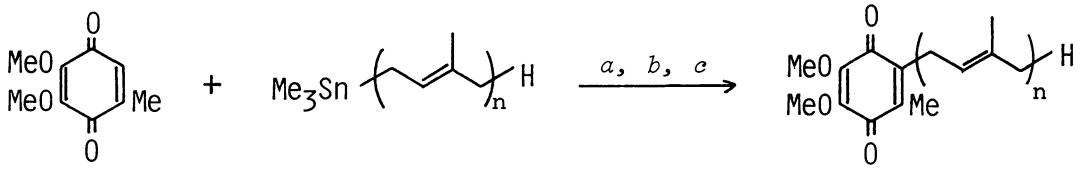
A new regio- and stereocontrolled synthesis of coenzyme Q_n (n=2, 3 9, 10) is described. Coupling of geranyltrimethyltin with 2,3-dimethoxy-5-methylbenzoquinone was successfully undertaken in the presence of BF_3OEt_2. After oxidation of the resulting mixture coenzyme Q_2 was obtained in 90% overall yield with >99% Δ^2-*trans* stereochemistry. Similary, all-*trans*-coenzyme Q_9 and Q_{10} were obtained in reasonable yields.

A series of coenzyme Q_n (ubiquinone-n) occurs in the majority of organisms from bacteria to higher plants and animals. It is known they are involved in respiratory and photosynthetic electron transport systems. Especially, coenzyme Q_{10} is known by its marked physiological and clinical activity (e.g. protecting from human congestive heart failure[2]). Various coupling methods have been tried to introduce polyprenyl side chain into quinone nucleus. Complete stereospecific synthesis required has not been fulfilled so far, because the double bonds in the side chain are hardly kept their trans configuration during the usual syntheses. For example, acid catalyzed direct condensation of 2,3-dimethoxy-5-methylbenzoquinone with polyprenyl alcohols suffers from the undesired cyclization to give chromanol in addition to the cyclization of isoprenyl side chain.[3] Reaction of π-allylnickel bromide complex with quinone (1)[4] or with a halide of masked quinone[5] also have been tried to obtain the target molecule. However, both methods provided unsatisfactory results both in yield and in stereoselectivity at Δ^2 position of polyprenyl group introduced.

In a previous work,[6] coenzyme Q_1 was selectively obtained by the coupling of prenyltributyltin and 1. We succeeded here in the regio- and stereocontrolled synthesis of coenzyme Q_n (n=2, 3, 9, and 10) (3a~e) employing the promising allylation reaction with polyprenyltrialkyltin. The following procedure for the preparation of *trans*-coenzyme Q_2 (3a) is representative of these reactions. To a dichloromethane solution (20ml) of 1 (182mg, 1.0mmol) was added BF_3OEt_2 (3mmol) under N_2 at -78°C. After a few

Scheme.



1 2 3

a, BF_3OEt_2, CH_2Cl_2, -78~-60°C; *b*, H_3O^+; *c*, Ag_2O, Et_2O

a, n=2
b, Δ^2-*cis*, n=2
c, n=3
d, n=9
e, n=10

Table. Regio- and Stereoselective Preparation of Coenzyme Q_n[a]

Run	2 (equiv. to 1)	Product, 3	%, Yield[b]	3, Stereochemistry at Δ^2, *tran/cis*
1	a (1.2)	Coenzyme Q_2	90(65)	>99/ 1
2	b (1.2)	*cis*-Coenzyme Q_2	79(70)	12/88
3	c (1.2)	Coenzyme Q_3	83(82)	83/17
4	d (0.85)	Coenzyme Q_9	(51)[c,d]	100/ 0
5	e (0.85)	Coenzyme Q_{10}	51(51)[c,d]	85/15

[a] Fully characterized by spectroscopic methods and elemental analysis. [b] Yields in parentheses are of purified products after isolation based on quinone. All others are determined by ^{1}H-NMR. [c] Corresponding amount of starting quinone was recovered. [d] Yield is determined based on the amount of polyprenyltin reagent.

minutes, geranyltrimethyltin[1] (2a) (360mg, 1.2mmol) was added dropwise over 5min period, and then the temperature of the resulting solution was elevated to -65°C within 1h. After usual quenching and extraction, the ethereal solution was treated with silver oxide to obtain crude mixture, which was purified by preparative TLC on silica gel; affording a yield of 65% (197mg) of pure coenzyme Q_2 (3a); ^{1}H-NMR(CCl_4); δ 1.55 (s,3H, terminal *trans*-CH_3), 1.62(s, 3H, terminal *cis*-CH_3), 1.76(s, 3H, *trans*-CH_3 nearest ring), 1.94(bs, 7H, ring CH_3 and CH_2CH_2), 3.11(d, 2H, Ar-CH_2, J=7Hz), 3.94(s, 6H, $2CH_3O$), 4.88 (t, 1H, CH=C, J=8Hz), 4.95(bs, 1H, CH=C). IR(neat); 2920(vs), 1640(vs, C=O), 1605(vs), 1445(vs), 1260(vs), 1202(vs), 1150(s), 1100(s), 1004(s), 940(m), 734cm^{-1}(s). Anal. ($C_{19}H_{26}O_4$) C, H.[9] *cis*,/*trans*-Coenzyme Q_2 can be assigned by ^{1}H-NMR chemical shifts[7] (δ 1.71 and 1.76, respectively) of CH_3 attached to the proximal double bond (Δ^2), and analyzed quantitatively by medium pressure LC (10μ-silica gel, 3.9mmX30cm + 7.8mmX30cm,

7% ether in hexane). The isomeric purity of synthetic 3a was determined to be *trans*:*cis* > 99:1.

Similarly, *cis*-coenzyme Q_2 (3b) was obtained in 79% yield, with retention of 88% cis configuration at Δ^2 position from neryltrimethyltin reagent (2b) (reagent grade: *trans*:*cis*=6:94). Trans selectivity in our synthetic method was also observed in the synthesis of coenzyme Q_3 (*trans*:*cis*=83:17) with 2c (reagent grade: *trans*:*cis*=60:40). These profitable chracteristics were utilized to the stereospecific synthesis of all-*trans*-coenzyme Q_9 and Q_{10} (run 4 and 5).[8] More diluted condition and a elevated temperature (-50~-40°C) were required to obtain optimum yields.

We also have attained stereospecific introduction of polyprenyl group into naphthoquinone nucleus.[1] In every case, any undesirable side reaction products mentioned above were not detected chromatographycally and spectroscopically (^{1}H-NMR).

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8) All-*trans*-soranesyltrimethyltin (2d) was prepared from all-*trans*-soranesyl bromide[3a] by the similar coupling method mentioned in reference 1. Decaprenyltrimethyltin (2e) was also obtained from decaprenyl bromide,[3a] which was determined to be *trans/cis*= 81∿82/19∿18 by 220MHz ^{1}H-NMR.

9) Found; C, 71.73; H, 8.26%. Calcd for $C_{19}H_{26}O_4$; C, 71.67; H, 8.23%.

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