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REGIOSELECTIVE POLYPRENYL REARRANGEMENT OF POLYPRENYL 2,3,4,5-TETRASUBSTITUTED PHENYL ETHERS PROMOTED BY BORON TRIFLUORIDE

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4-Acetoxy-6-polyprenyl-2,3,5-trimethylphenols or 2,3-dimethoxy-5-methyl-6-polyprenylhydroquinones were obtained selectively by the $BF_3 \cdot OEt_2$ catalyzed polyprenyl rearrangement of polyprenyl 4-acetoxy-2,3,5-trimethylphenyl ethers or polyprenyl 2,3-dimethoxy-4-hydroxy-5-methylphenyl ethers.

It is known that isoprenoid quinones play an important role in biological processes such as electron transport, blood clotting, and oxidative phosphorylation. Although various coupling methods have been tried to introduce polyprenyl side chains into quinone nucleus,$^{1)}$ the yields are not satisfactory owing to by-products formation.$^{2)}$

Recently Naruta and Maruyama$^{3)}$ succeeded in the regio- and stereocontrolled synthesis of coenzyme Q_n(ubiquinone-n) employing the promising allylation of quinones with polyprenylalkyltin.

In this paper, we wish to report the introduction of polyprenyl groups into aromatic ring by the regioselective polyprenyl rearrangement of polyprenyl aryl ethers.

Polyprenyl aryl ethers (3a-e) were easily prepared by the reaction of 4-acetoxy-2,3,5-trimethylphenol with the corresponding polyprenyl bromides$^{4)}$ under basic condition.$^{5)}$

The rearrangement of polyprenyl groups was carried out in the presence of Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, $AlCl_3$, or $ZnCl_2$, dramatic catalysis by $BF_3 \cdot OEt_2$ being observed.$^{6)}$ Thus, when $BF_3 \cdot OEt_2$ was added to CCl_4 solution of 3e (Δ^2:E/Z=99/1) at -15°C, the reaction completed within 15min giving 4-acetoxy-6-decaprenyl-2,3,5-trimethylphenol [4e(Δ^2:E/Z$>$99/1)] in 80% yield without any detectable formation of undesirable isomers (Table 1, entry 5).

Similarly, a series of Δ^2-E-(or E-rich)-polyprenyl aryl ether (3) with n=2,3, and 9 afforded the corresponding rearranged products in 40-76% yields (Table 1, entry 1,3, and 4).

However, when Δ^2-Z-isomers were used under the same conditions, the corresponding rearranged products with 85-6% retention of Z-configuration at Δ^2 position were isolated in 16-26% yields (Table 1, entry 2 and 6).

Scheme 1

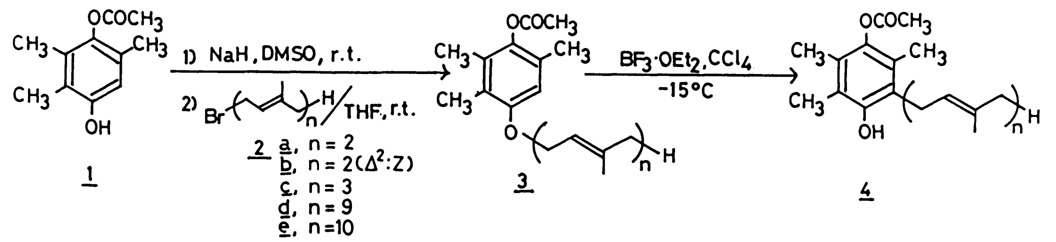


Table 1. Polyprenyl rearrangement of 3[a]

Entry		Polyprenyl aryl ether, 3 Stereochemistry at Δ^2 E/Z[b]	Product, 4 Isolated yield %[c]	Product, 4 Stereochemistry at Δ^2 E/Z[b]
1	a	98/2	76	>99/1
2	b	5/95	26	19/81
3	c	60/40	40	84/16
4	d	99/1	69	>99/1
5	e(Δ^2:E)[d]	99/1	80	>99/1
6	e(Δ^2:Z)[d]	0/100	16	14/86

a) Fully characterized by spectroscopic methods. b) The ratio was determined by HPLC [LiChrosorb Si 60 (5μm), ϕ4mm x 250mm, n-hexane/diisopropyl ether (5/1)]. c) Yield is determined based on the amount of 3. d) 3e(Δ^2:E) and 3e(Δ^2:Z) were isolated from their mixture (3e) by column chromatography on silica gel [eluted with n-hexane/diisopropyl ether (7/3)].

These results indicate the present procedure affords a convenient route for the preparation of naturally occurring coenzyme Q_n. Thus the reaction of 7a-e was next examined. Compounds 7a-e were obtained by the hydrolysis of polyprenyl 4-benzoyloxy-2,3-dimethoxy-5-methylphenyl ethers (6a-e).[7)]

Compounds 7a-e could also enter into the reaction to give 8a-e which, without isolation, were oxidized (MnO_2) to 9a-e [coenzyme Q_n(n=2,3,9,and 10)] in 35-85% yields (Table 2).

Scheme 2

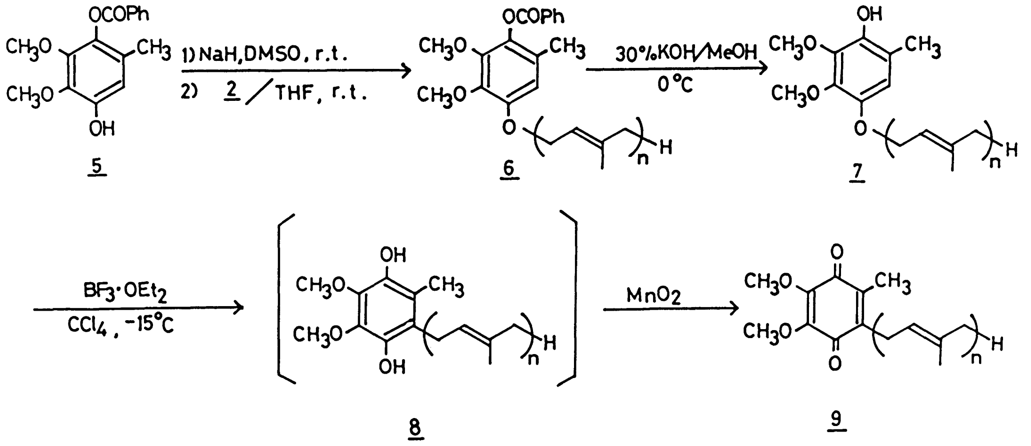
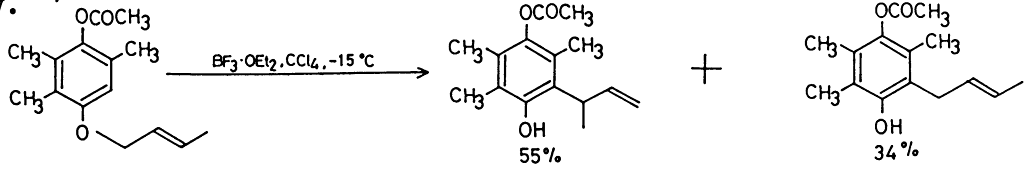


Table 2. Polyprenyl rearrangement of 7[a]

Entry	7[b]	Product, 9	Isolated yield %[c]	9, Stereochemistry at Δ^2 E/Z[d]
1	a	Coenzyme Q_2	43[e]	>99/1
2	c	Coenzyme Q_3	35 (69[e])	89/11 (82/18[e])
3	d	Coenzyme Q_9	85	97/3
4	e	Coenzyme Q_{10}	50 (33[e])	91/9 (85/15[e])

a) Fully characterized by spectroscopic methods. b) The stereochemistry at Δ^2 position of 7a-e could not be determined because their isomers have the same retention time. c) Yield is determined based on the amount of 7. d) The ratio was determined by HPLC under the same conditions described before. e) Ethyl ether was used as a solvent. In the case of 7e, the reaction was carried out at -15-0°C (no reaction took place at -15°C).

Contrary to the case of polyprenyl aryl ethers, 2-butenyl (4-acetoxy-2,3,5-trimethylphenyl ether (10)[8] afforded both 11[9] and 12[10] in 55% and 34% yields, respectively.[11]



10 11 12

The following procedures are representative.

Preparation of 4-acetoxy-6-decaprenyl-2,3,5-trimethylphenol [4e(Δ^2:E)] and 2,3-dimethoxy-5-methyl-6-solanesyl-1,4-benzoquinone (9d) ----- To a solution of 3e (Δ^2:E) (340mg,0.39mmol) in CCl_4(3ml), $BF_3 \cdot OEt_2$(0.60mmol) was added under nitrogen atmosphere at -15°C. After 15min, aquous saturated NaCl solution was added and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated. The stereochemistry at Δ^2 position of the resulting crude product was determined to be E/Z>99/1 by HPLC [LiChrosorb Si 60 (5μm), Ø4mm x 250mm, n-hexane/diisopropyl ether (5/1)]. The product was purified by column chromatography on silica gel [eluted with n-hexane/diisopropyl ether (7/3)] affording pure 4e (Δ^2:E) in 80% (271mg) yield. ; ^{1}H-NMR ($CDCl_3$) δ 1.89(33H,CH_3), 2.02-2.30 (45H,CH_2CH_2 and ring CH_3), 2.33(s,3H,CH_3CO), 3.38(d,2H,Ar-CH_2,J=7Hz),5.09(s,1H,OH), 4.89-5.40(br,10H,CH=C) ppm ; IR (neat) ν_{max} 3550(OH), 2920, 1750, 1460, 1390, 1235, 1220, 1080 cm^{-1}.

In the case of using 7d as a starting material, to a solution of 7d (200mg, 0.25mmol) in CCl_4(2ml), $BF_3 \cdot OEt_2$(0.37mmol) was added under nitrogen atmosphere at -15°C. After 10min, the reaction mixture was quenched with aquous saturated NaCl solution. The organic layer was separated from the quenched reaction mixture and washed with water. It was dried over $MgSO_4$ and subsequent oxidation with excess activated MnO_2 (200mg) afforded crude 9d. The stereochemistry at Δ^2 position of the crude product was determined to be E/Z=97/3 by HPLC analysis under the same conditions described above. The product was purified by column chromatography on silica gel [eluted with n-hexane/diisopropyl ether (7/3)] affording pure 9d in 85% (170mg) yield. ; ^{1}H-NMR ($CDCl_3$) δ 1.60(24H,CH_3), 1.67(s,3H,CH_3), 1.74(s,3H,CH_3), 2.00(bs,35H,CH_2CH_2 and ring CH_3), 3.19(d,2H,Ar-CH_2,J=7 Hz), 4.00(s,6H,2CH_3O), 4.90-5.20(br,9H,CH=C) ppm ; IR (neat) ν_{max} 2920, 1640, 1605, 1450, 1380,1285, 1265, 1205, 1100 cm^{-1}.

In conclusion, the $BF_3 \cdot OEt_2$ promoted regioselective polyprenyl rearrangement of polyprenyl aryl ethers provides a convenient route for the preparation of polyprenyl substituted phenols.

References

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2) R. Rüegg, U. Gloor, R. N. Goel, R. Ryser, O. Wiss, and O. Isler, Helv. Chim. Acta , 42, 2616 (1959); W. E. Wolf, C. H. Hoffman, N. R. Trenner, B. H. Arison, C. H. Shunk, B. O. Linn, J. F. McPherson, and K. Folkers, J. Am. Chem. Soc., 80, 4752 (1958); R. A. Morton, U. Gloor, O. Schinrler, W. M. Wilson, L. H. Chopardolit-Jean, F. W. Hemming, O. Isler, W. F. Leat, J. F. Pennock, R. Rüegg, U. Schwieter, and O. Wiss, Helv. Chim. Acta , 41, 2343 (1958).

3) Y. Naruta and K. Maruyama, Chem. Lett., 881 (1979); idem., ibid., 885 (1979).

4) Polyprenyl bromides were prepared by the reaction of geraniol, nerol, farnesol, solanesol, or isodecaprenol with PBr_3 in ethyl ether, and used without further purification.

5) The yields of 3a, 3b, 3c, 3d, and 3e from 2 were 65%, 50%, 65%, 90%, and 72%, respectively.

6) In the case of using $TiCl_4$, compounds 3 were decomposed completely. The reaction of 3d or 3e (Δ^2:E/Z=75/25) in the presence of $AlCl_3$ or $ZnCl_2$ afforded the rearranged product in low yield. Further studies are now in progress.

7) The yields of 7a, 7c, 7d, and 7e from 2 were 63%, 41%, 73%, and 80%, respectively.

8) ^{1}H-NMR (CCl_4) δ 1.80(m,3H), 2.10(s,3H), 2.17(s,6H), 2.33(s,3H,CH_3CO), 4.50(m,2H,CH_2), 5.80(m,2H,C=CH-), 6.66(s,1H,aromatic) ppm ; IR (neat) ν_{max}2925, 1760, 1490, 1380, 1230, 1200 cm^{-1}.

9) ^{1}H-NMR (CCl_4) δ 1.45(d,2H), 2.03(s,3H), 2.10(s,6H), 2.30(s,3H,CH_3CO), 3.60-4.15(m,1H), 5.15-5.60(m,2H,C=CH_2), 5.60(s,1H,OH), 6.06-6.60(1H,-CH=) ppm ; IR (neat) ν_{max} 3500(OH), 2970, 1760, 1460, 1380, 1220 cm^{-1}.

10) ^{1}H-NMR (CCl_4) δ 1.60(m,3H), 2.03(s,6H), 2.10(s,3H), 2.30(s,3H,CH_3CO), 3.30 (m,2H,CH_2), 5.10(s,1H,OH), 5.55(m,2H,-CH=C-) ppm ; IR (neat) ν_{max} 3500(OH), 2925, 1740, 1460, 1380,1220 cm^{-1}.

11) Mukaiyama, et al. have reported the Claisen rearrangement of substituted allyl phenyl ethers in the presence of $TiCl_4$-$Ti(OPr^i)_4$ [K. Narasaka, E. Bald, and T. Mukaiyama, Chem. Lett., 1041 (1975)].

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