Highly S_N2'-, (*E*)-, and Antiselective Alkylation of Allylic Phosphates. Facile Synthesis of Coenzyme Q_{10}

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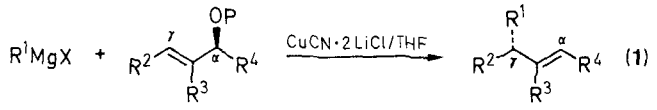
Dedicated to Professor H.J. Bestmann in recognition of his contribution as Executive Editor of Synthesis

Treatment of secondary allylic chlorides or allylic phosphates in tetrahydrofuran with prenyl Grignard reagent in the presence of CuCN · 2 LiCl gave geraniol or farnesol derivatives with high S_N2' selectivity. Phosphate leaving groups were highly *trans*-stereoselective for the formation of (*E,E*)-farnesol derivatives. Furthermore, complete anti-S_N2' selectivity was observed in the alkylation of optically active allylic phosphates. The present method appears to be an excellent carbon-carbon coupling reaction with high regio-, (*E*)-, and enantioselectivity. Coenzyme Q_{10} (ubiquinone 10) was efficiently synthesized using this methodology.

The substitution reaction on allylic carbon is one of the most important processes in organic synthesis. During the past decade, organocopper reagents leading to S_N2 or S_N2' coupling products have been intensively studied.[1] Organocuprates generally show γ-anti selectivity in reaction with allylic carboxylates[2] and allylic sulfonates.[3,4] Recently γ-syn-substitution preference has been observed with allylic carbamates,[5,6] allyloxybenzothiazoles,[7] and allylic ammonium salts.[8] Although these processes are extremely useful and broadly utilized in organic synthesis,[9] there are still drawbacks and limitations to each of the known procedures. Here, we wish to report that the phosphate ester was shown to be the leaving group of choice in the remarkable S_N2'-, (*E*)-, and antiselective reaction between Grignard reagent and allylic alcohol derivatives in the presence of a copper(I) salt (eq. 1).[10] Coenzyme Q_{10} (ubiquinone 10) was efficiently synthesized with this methodology.



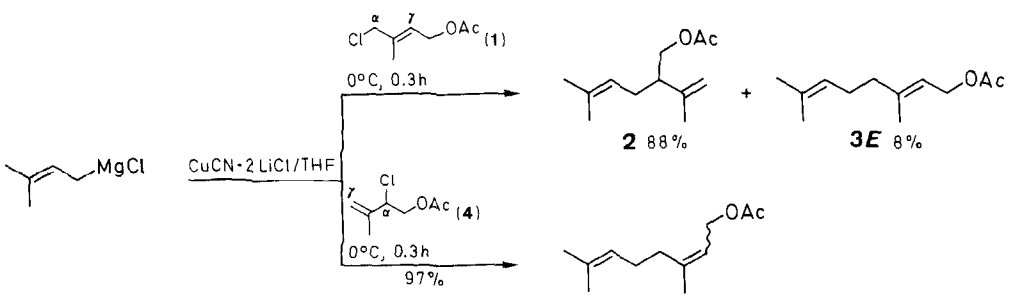
(1)

Treatment of the primary allylic chloride **1**[11] in THF with prenyl Grignard reagent in the presence of CuCN · 2 LiCl[12] at 0 °C for 20 minutes gave lavandulyl acetate (**2**) in 88% yield with a small amount of geranyl acetate (**3E**). Similarly, reaction with the secondary allylic chloride **4**[13] afforded neryl acetate (**3Z**) with moderate stereoselectivity in 97% yield (Scheme **1**). Thus, the process exhibited a S_N2' coupling preference for the allylic organomagnesium-copper complex with allylic chloride.

In an attempt to improve *E,Z*-stereoselectivity of this process, an extensive study was made of the effect of leaving groups on stereoselectivity.[14] Some of our results of allylic derivatives **5**[13,15] are summarized in Table 1. The phosphate leaving group is much more convenient and general than a variety of other derivatives. It also solves the problem of stereoselectivity (*E*/*Z* = 96:4, γ/α = > 99:1, entries 3–5).[17] It should be noted that the other ester derivatives such as mesylate derivatives did not result in high stereoselectivity (entries 8 and 9) despite that reported for α,β-enoates systems.[3] With primary allylic phosphate **9**,[18] S_N2' coupling was still dominant (Table 2). No remarkable differences in γ/α selectivities, however, were observed among the allylic phosphates **9a–9c** for prenylation (entries 1–3). Butylation of **9a** afforded a better regioselectivity (γ/α = 96:4, entry 4).

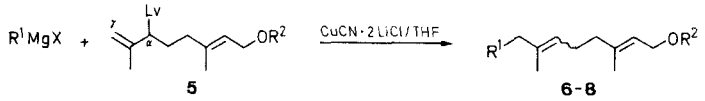
If the displacement is stereospecific it will result in a predictable transfer of chirality from the secondary alcohol center to a newly formed carbon atom. The stereochemical results for prenylation and butylation of (*R*)-allylic phosphate **12** with Grignard reagent and CuCN · 2 LiCl are shown in entries 1 and 2 of Table 3. Synthesis of the chiral substrate **12** was accomplished in three steps from (*E*)-2-butenal (**20**) as shown in Scheme **2**. (*R*)-Allylic alcohol **21** (94% ee) was obtained by Sharpless kinetic resolution[20] of the corresponding racemic allylic alcohol (±)-**21**. The prenylated product **16** was found to be homogeneous by capillary GC, and was shown to be a complete 1,3-chirality transfer by 500 MHz ^{1}H-NMR analysis using the shift reagents, Ag(fod) and Eu(tfc)$_3$.[21] The absolute stereochemistry of the product was shown to have the *S* configuration by ozonolysis/$LiAlH_4$ reduction (eq. 2);[22] thus, in this acyclic system, the enantioselectivity of the reaction was nearly quantitative (corrected).[23] Similarly, the enantioselective butylation of **12** was accomplished with equal efficiency (entry 2, Table 3).[24]

The phosphate system is similarly advantageous in a cyclic system (entries 3–5, Table 3). The result of prenylation of (+)-*trans*-carvyl chloride (**13**)[25] and the corre-



Scheme 1

Table 1. The Effect of Leaving Groups of Secondary Allylic Alcohol Derivatives on γ/α Regio- and E/Z Stereoselectivity

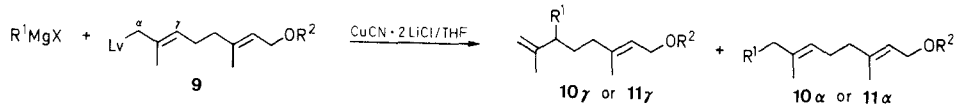


5 6-8

Entry	R^1MgX	Substrate	Lv	R^2	Reaction Temp. (°C)	Reaction Time (h)	Product	Yield[a] (%)	γ/α[b] Ratio	E/Z[b] Ratio
1	$(CH_3)_2C{=}CHCH_2MgCl$	**5a**	Cl	Ac	0	1	**6**	90	>99:1	46:54
2	$(CH_3)_2C{=}CHCH_2MgCl$	**5a**	Cl	Ac	−100	1	**6**	74	>99:1	85:15
3	$(CH_3)_2C{=}CHCH_2MgCl$	**5b**	$(EtO)_2PO_2$	Si(*t*-Bu)Me_2	−78	1	**7**	94	>99:1	96:4
4	$(CH_3)_2C{=}CHCH_2MgCl$	**5c**	$(i\text{-}PrO)_2PO_2$	Si(*t*-Bu)Me_2	−78	1	**7**	96	>99:1	96:4
5	$(CH_3)_2C{=}CHCH_2MgCl$	**5d**	$(c\text{-}C_6H_{11}O)_2PO_2$	Si(*t*-Bu)Me_2	−60	1	**7**	58	>99:1	96:4
6	$(CH_3)_2C{=}CHCH_2MgCl$	**5e**	$(PhO)_2PO_2$	Si(*t*-Bu)Me_2	−78	1	**7**	91	>99:1	74:26
7	$(CH_3)_2C{=}CHCH_2MgCl$	**5f**	$(Me_2N)_2PO_2$	Si(*t*-Bu)Me_2	−20	1.5	**7**	47	>99:1	59:41
8	$(CH_3)_2C{=}CHCH_2MgCl$	**5g**	MsO	Si(*t*-Bu)Me_2	−78	1	**7**	68	>99:1	55:45
9	BuMgCl	**5g**	MsO	Si(*t*-Bu)Me_2	−78	1	**8**	87	>99:1	53:47

[a] Yield after isolation and purification.
[b] Determined by GC analysis. For the entries 3–9, the ratios were determined after conversion to the corresponding alcohols.

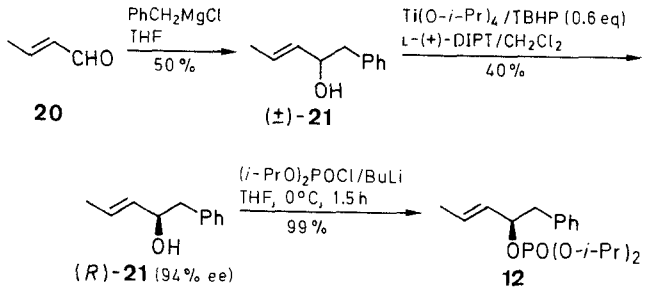
Table 2. The Effect of Leaving Groups of Primary Allylic Phosphates on γ/α Regioselectivity



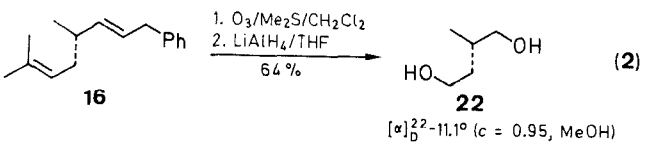
9 10γ or 11γ 10α or 11α

Entry	R^1MgX	Substrate	Lv	R^2	Reaction Temp. (°C)	Reaction Time (h)	Product	Yield[a] (%)	γ/α[b] Ratio
1	$(CH_3)_2C{=}CHCH_2MgCl$	**9a**	$(PhO)_2PO_2$	Ac	−78	1	**10**	95	88:12
2	$(CH_3)_2C{=}CHCH_2MgCl$	**9b**	$(EtO)_2PO_2$	Ac	−50	1	**10**	95	87:13
3	$(CH_3)_2C{=}CHCH_2MgCl$	**9c**	$(i\text{-}PrO)_2PO_2$	Ac	−40	1.5	**10**	82	88:12
4	BuMgCl	**9d**	$(PhO)_2PO_2$	Si(*t*-Bu)Me_2	−60	0.5	**11**	87	96:4

[a] Yield after isolation and purification.
[b] Determined by GC analysis.



Scheme 2

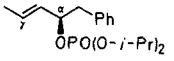
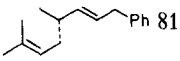
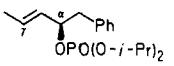
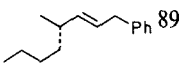
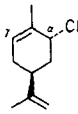
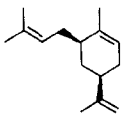
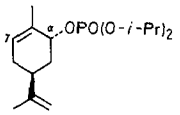
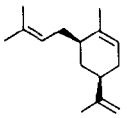
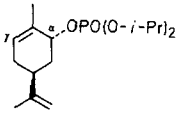
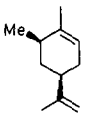
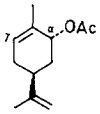
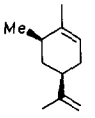


(2)

sponding diisopropyl phosphate **14**[26] with prenyl Grignard reagent/CuCN · 2 LiCl gave the γ- and antiselectivity (entries 3 and 4), and higher regio- and stereoselectivity are observed with phosphate. The diastereo selectivity (*cis*/*trans* ratio) of the prenylated product was determined by GC analysis using authentic *cis* isomer **18** and *trans* isomer **25**. Optically pure **18** and **25** were prepared by Wittig reaction from chiral aldehyde **23** and **24**,[27] respectively (Scheme 3). The γ/α selectivity of **18** was calculated from the optical purity of the major *cis* isomer. Methylation of **14** with MeMgI is also completely regio- and stereoselective (entry 5).[26,28] With the corresponding acetate **15**, however, no methylation reaction occurred even at 20 °C (entry 6).

The potential of the present methodology for the synthesis of polyprenoids is demonstrated by the synthesis of coenzyme Q_{10} (ubiquinone 10, **26**) which is known as a biologically active compound. Although various synthetic methods[29–31] were developed, most of these encountered problems in the construction of the all-*trans* decaprenyl side chain. In an attempt to develop a convenient approach for the total synthesis of coenzyme Q_{10}

Table 3. S_N2'-, (*E*)-Stereo-, and Antiselective Alkylation of Chiral Allylic Alcohol Derivatives

Entry	RMgX	Substrate	Reaction Temp. (°C)	Reaction Time (h)	Product	Yield[a] (%)	γ/α Ratio	*E*/*Z*[b] Ratio	Enantio- or Diastereoselectivity
1	$(CH_3)_2C{=}CHCH_2MgCl$	**12** 	−60	1	**16** 	81	>99:1[b]	>99:1	97:3[c]
2	BuMgCl	**12** 	−60	1	**17** 	89	>99:1[b]	>99:1	95:5[c]
3	$(CH_3)_2C{=}CHCH_2MgCl$	**13** 	−40	2.5	**18** 	90	87:13[d]		96:4[b]
4	$(CH_3)_2C{=}CHCH_2MgCl$	**14** 	−30	1.5	**18** 	63	96:4[d]		>99:1[b]
5	MeMgI	**14** 	−30	1	**19** 	85	>99:1[d]		>99:1[b]
6	MeMgI	**15** 	20	9	**19** 	<1	–		–

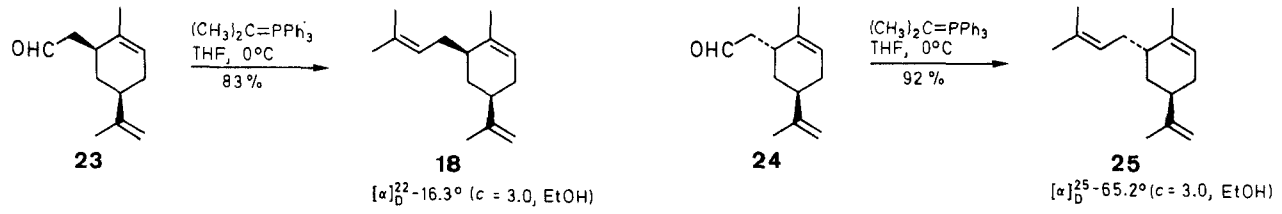
[a] Yield after isolation and purification.
[b] Determined by GC analysis.
[c] Determined by 500 MHz ^{1}H-NMR spectroscopy with Eu(tfc)$_3$ and Ag(fod).
[d] Calculated form the optical purity of the major *cis* isomer.

Table 4. Characterization of Products **8**, **10**, **11**, and **16–19**

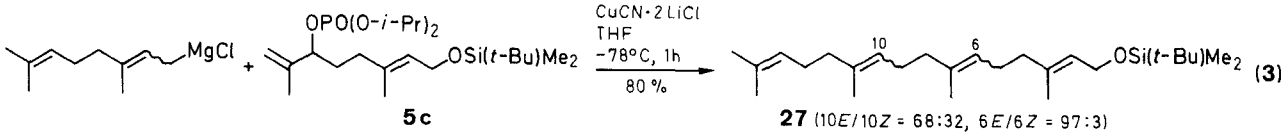
Product	R_f (solvent)	$[\alpha]_D^{20}$ (*c*, solvent)[a,b]	Molecular Formula[c]	IR (neat or CCl_4)[d] ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
8	0.76 (Hx/EtOAc, 3:1)	–	$C_{20}H_{40}OSi$ (324.6)	2980, 2950, 2880, 1470, 1260, 1120, 1080	0.07 (s, 6H), 0.86 (t, 3H), 0.90 (s, 9H), 1.1–1.5 (m, 6H), 1.58 (s, 3H), 1.65 (s, 3H), 1.9–2.2 (m, 6H), 4.19 (d, 2H, *J* = 6.2), 5.09 (t, 1H, *J* = 7.0), 5.30 (t, 1H, *J* = 6.4)
10	0.40 (Hx/EtOAc, 10:1)	–	$C_{17}H_{28}O_2$ (264.4)	3090, 2990, 2950, 1740, 1450, 1380, 1240, 1030	1.3–1.8 (m, 2H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 6H), 1.8–2.2 (m, 5H), 2.06 (s, 3H), 4.58 (d, 2H, *J* = 7.2), 4.67 (s, 1H), 4.75 (s, 1H), 5.05 (m, 1H), 5.30 (t, 1H, *J* = 7.0)
11	0.76 (Hx/EtOAc, 3:1)	–	$C_{20}H_{40}OSi$ (324.6)	2950, 2880, 1470, 1390, 1260, 1110, 1080	0.07 (s, 6H), 0.87 (t, 3H, *J* = 5.4), 0.90 (s, 9H), 1.1–1.5 (m, 8H), 1.58 (s, 3H), 1.60 (s, 3H), 1.8–2.1 (m, 3H), 4.19 (d, 2H, *J* = 6.4), 4.67 (s, 1H), 4.74 (s, 1H), 5.28 (t, 1H, *J* = 6.6)
16	0.43 (Hx)	−5.85 (1.33, $CHCl_3$)	$C_{16}H_{22}$ (214.4)	3060, 2990, 2940, 1510, 1430, 1390, 980	1.00 (d, 3H, *J* = 6.0), 1.70 (s, 3H), 1.80 (s, 3H), 2.00 (t, 2H, *J* = 6.0), 2.1–2.3 (m, 1H), 3.35 (d, 2H, *J* = 5.0), 5.15 (t, 1H, *J* = 7.5), 5.1–5.4 (m, 2H), 7.1–7.4 (m, 5H)
17	0.44 (Hx)	+15.79 (2.06, EtOH)	$C_{15}H_{22}$ (202.3)	3050, 2975, 2940, 2875, 1500, 1460, 1385	0.89 (t, 3H, *J* = 6.6), 0.98 (d, 3H, *J* = 6.6), 1.2–1.4 (m, 6H), 2.0–2.2 (m, 1H), 3.34 (d, 1H, *J* = 6.2), 5.40 (dd, 1H, J_1 = 7.0, J_2 = 15.4), 5.53 (dt, 1H, J_1 = 6.0, J_2 = 15.2), 7.2–7.4 (m, 5H)
18	0.54 (Hx)	−15.05[f] (3.10, EtOH)	$C_{15}H_{24}$ (204.4)	3090, 2970, 2920, 2860, 1650, 1460, 1380	1.62 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 1.72 (s, 3H), 1.7–2.4 (m, 8H), 4.70 (s, 2H), 5.10 (t, 1H, *J* = 7.5), 5.48 (m, 1H)
19	0.59 (Hx)	−32.61 (1.37, MeOH)	$C_{11}H_{18}$ (150.3)	3100, 2980, 2925, 2870, 1650, 1550, 1455, 1445, 1380	1.04 (d, 3H, *J* = 7.0), 1.68 (s, 3H), 1.75 (s, 3H), 1.8–2.3 (m, 6H), 4.70 (s, 2H), 5.4 (m, 1H)

[a] Measured using a JASCO DIP-140 polarimeter.
[b] Hx = hexane.
[c] Satisfactory microanalysis obtained: C ± 0.44, H ± 0.35.
[d] Recorded on a Hitachi 260-10 Infrared spectrometer.
[e] Obtained on a Varian Gemini-200 spectrometer at 200 MHz.
[f] Value of entry 4 in Table 3.

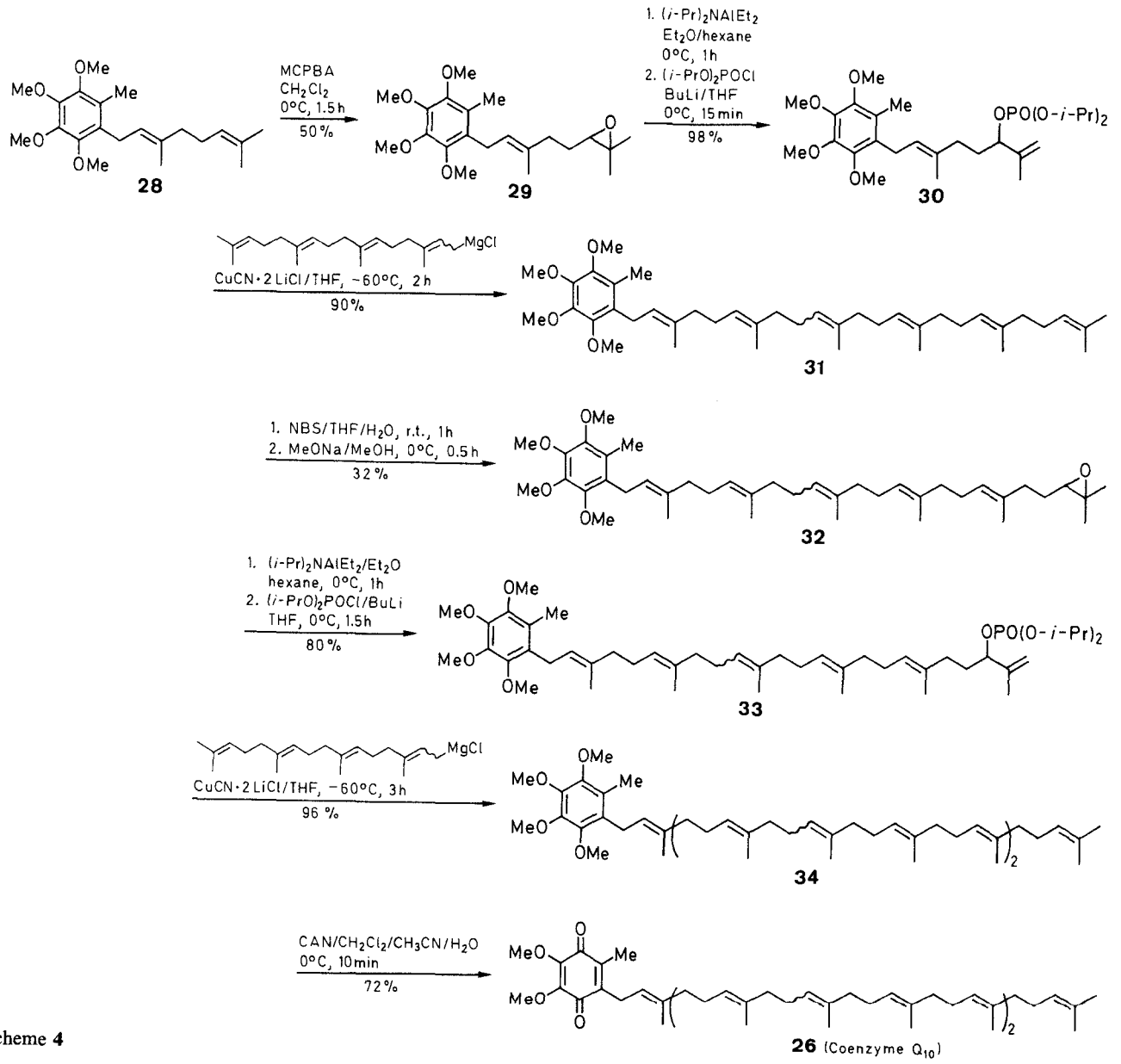
we investigated the stereoselectivity of the coupling reaction between geranyl Grignard reagent and secondary allylic phosphate **5c** (eq. 3). Geranylgeraniol derivative **27** was predominantly formed in this reaction and the *E*/*Z* ratio of the C_{10}–C_{11} double bond was 68:32, whereas that of the C_6–C_7 was 97:3.



Scheme 3



Synthesis of coenzyme Q_{10} (**26**) could be directly carried out from reported intermediate **28**[32] by two additions of geranylgeranyl Grignard reagent (Scheme **4**). This coenzyme Q_2 type compound **28** was converted to the allylic phosphate **30** by a three-step sequence: (1) epoxidation with 3-chloroperoxybenzoic acid (MCPBA);[30] (2) isomerization to allylic alcohol;[16] (3) phosphorylation. Treatment of **30** in THF with geranylgeranyl Grignard reagent in the presence of CuCN · 2LiCl at −60 °C afforded coenzyme Q_6 derivative **31** in 90% yield. Compound **31** was converted via the terminal monobromohydrin into the epoxide **32** in 32% yield.[33] The same



Scheme 4

sequence of synthesis of the allylic phosphate **33** from **32** followed by coupling reaction with geranylgeranyl Grignard reagent yielded a precursor of coenzyme Q_{10} **34**.[30,31] Finally, deprotection of **34** with ceric ammonium nitrate (CAN) gave coenzyme Q_{10} **(26)** in 72% yield. This product was recrystallized twice (mp 46.5–47°C, Lit.[30] mp 47°C) and was found to be identical with the authentic specimen[34] as judged by comparison of the spectral properties (IR, ^{1}H-NMR) and thin-layer chromatographic behavior.

In summary, the method described here appears to be an excellent carbon-carbon coupling reaction with high regio-, (*E*)-, and enantioselectivity.[35] Main features of the present scheme are: (1) exclusive S_N2' substitution with anti attack on both acyclic and cyclic allylic systems; (2) acyclic allylic phosphates are transformed into (*E*)-alkenes; (3) prenyl carbanion reacts at the less substituted allyl terminus; (4) optically active allylic phosphate can be simply prepared from the corresponding alcohol which, in turn, is easily obtained from readily available chiral ethynyl carbinol. Many difficulties, however, are encountered in the preparation of the corresponding chloride or mesylate.

IR spectra were obtained using a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were obtained using a Varian Gemini-200 (200 MHz) or VXR-500S (500 MHz) spectrometer. Analytical gas chromatography (GC) was performed on Shimadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (25 m) using nitrogen as carrier gas. TLC was done on silica gel (Merck Silica 60 F_{254} sheets). Silica gel was purchased from Merck (silica gel 60, 230–400 mesh). Optical rotation was measured on a JASCO DIP-140 polarimeter. All experiment were carried out under an atmosphere of dry argon.

(2*E*,6*E*)-1-*tert*-Butyldimethylsiloxy-3,7,11-trimethyl-2,6,10-dodecatriene (7); Typical Procedure:

To a solution of 3-methyl-2-butenylmagnesium chloride, prepared from magnesium turnings (365 mg, 15.0 mmol) and 1-chloro-3-methyl-2-butene (314 mg, 3.0 mmol) in THF (10 mL), is added a solution of CuCN (269 mg, 3.0 mmol) and LiCl (254 mg, 6.0 mmol) in THF (3 mL) at 0°C and the resulting dark violet solution is stirred at 0°C for 30 min. The mixture is then cooled to −78°C and a solution of the allylic diisopropylphosphate **5c** (449 mg, 1.0 mmol) in THF (2 mL) is added at −78°C. The solution is stirred at this temperature for 1 h, then quenched with sat. NH_4Cl solution (15 mL). Et_2O (15 mL) is then added and the organic phase is separated, washed with brine (15 mL), and dried ($MgSO_4$). The solvent is evaporated and the crude product is purified by column chromatography on silica gel to give **7** (323 mg, 96%), the *E*/*Z* ratio was determined to be 96:4 by GC after converting to farnesol (Bu_4NF/THF).

1-[(2*E*)-6,7-Epoxy-3,7-dimethyloct-2-enyl]-2,3,4,5-tetramethoxy-6-methylbenzene (29):

To a solution of **28** (3.80 g, 10.9 mmol) in CH_2Cl_2 (30 mL) is added a solution of MCPBA (80% purity, 3.07 g, 14.2 mmol) in CH_2Cl_2 (30 mL) at 0°C over 30 min. The reaction mixture is stirred at 0°C for 1 h, quenched with sat. aq $NaHCO_3$, and then with H_2O, and dried ($MgSO_4$). The solvent is evaporated and the crude product is purified by column chromatography on silica gel using a 5:1 mixture of hexane and Et_2O as eluant to give **29** as a colorless oil; yield: 1.99 g (50%); R_f 0.48 (hexane/Et_2O, 1:1).

$C_{21}H_{32}O_5$	calc.	C 69.20	H 8.85
(364.5)	found	69.41	8.99

IR (CCl_4): ν = 3000, 2970, 2900, 1475, 1419, 1120, 1057 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.24 (s, 3H), 1.26 (s, 3H), 1.5–1.7 (m, 2H), 1.79 (s, 3H), 2.0–2.3 (m, 2H), 2.14 (s, 3H), 2.68 (t, 1H, J = 6.2 Hz), 3.33 (d, 2H, J = 6.6 Hz), 3.79 (s, 6H), 3.91 (s, 6H), 5.10 (t, 1H, J = 6.9 Hz).

Diisopropyl [(4*E*)-1-Isopropenyl-4-methyl-6-(2,3,4,5-tetramethoxy-6-methylphenyl)-4-hexenyl]phosphate (30):

To a solution of (*i*-Pr)$_2$NAlEt$_2$[16] in Et_2O/hexane (25 mmol, 82 mL) is added a solution of oxirane **29** (1.99 g, 5.46 mmol) in hexane (17 mL) at 0°C drop by drop over a period of 30 min. The mixture is stirred at this temperature for 30 min, quenched with ice-cooled 1N HCl (100 mL). Et_2O (50 mL) is then added and the organic phase is separated, washed with brine (100 mL), and dried ($MgSO_4$). The solvent is evaporated and to a solution of the crude product in THF (20 mL) is added a solution of BuLi in hexane (1.61 M, 3.73 mL, 6.01 mmol) dropwise using a syringe at −78°C. After stirring at this temperature for 10 min and then at 0°C for 10 min, diisopropyl chlorophosphate (2.0 g, 10 mmol) is added at 0°C and stirred at this temperature for 15 min. The mixture is quenched with sat. aq NH_4Cl (20 mL) and the resulting organic layer is separated. The aqueous layer is extracted with Et_2O (20 mL). The combined organic layers are dried ($MgSO_4$) and concentrated. The crude product is purified by column chromatography on silica gel using a 1:4 mixture of hexane and Et_2O as eluant to give **30** as a colorless oil; yield: 2.83 g (98%); R_f 0.20 (hexane/Et_2O, 1:2).

$C_{27}H_{45}O_8P$	calc.	C 61.35	H 8.58
(528.6)	found	61.29	8.83

IR (KBr): ν = 2975, 2925, 1655, 1462, 1403, 1258, 1105, 1038, 994 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.3–1.4 (m, 12H), 1.71 (s, 3H), 1.77 (s, 3H), 1.6–2.0 (m, 4H), 2.13 (s, 3H), 3.31 (d, 2H, J = 6.3 Hz), 3.79 (s, 6H), 3.90 (s, 3H), 3.91 (s, 3H), 4.5–4.7 (m, 3H), 4.89 (s, 1H), 4.96 (s, 1H), 5.05 (t, 1H, J = 6.6 Hz).

1-[(2*E*,6*E*,10*E*,14*E*,18*E*)-3,7,11,15,19,23-Hexamethyl-2,6,10,14,18,22-tetracosahexaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (31):

To a solution of geranylgeranylmagnesium chloride, prepared from magnesium turnings (3.65 g, 150 mmol) and geranylgeranyl chloride (9.27 g, 30 mmol) in THF (30 mL), is added a solution of CuCN (3.28 g, 36.6 mmol) and LiCl (3.03 g, 71.5 mmol) in THF (30 mL) at −30°C and the mixture is stirred at this temperature for 10 min and then at 0°C for 20 min. The resulting black solution is cooled to −78°C and a solution of **30** (1.59 g, 3.01 mmol) in THF (2 mL) is added dropwise using a syringe at −78°C. The solution is stirred at −60°C for 2 h, then quenched with 2N HCl solution (80 mL). The organic layer is separated and the aqueous layer is extracted with Et_2O (50 mL). The combined organic layers are washed with 2N NaOH solution (80 mL) and brine (80 mL), and then dried ($MgSO_4$). The solvent is evaporated and the crude product is purified by column chromatography on silica gel (150 g, hexane/Et_2O, 20:1 ~ 10:1) to give **31** as a colorless oil; yield: 1.69 g (90%); R_f 0.29 (hexane/Et_2O, 10:1).

$C_{41}H_{64}O_4$	calc.	C 79.30	H 10.39
(621.0)	found	78.98	10.53

IR (KBr): ν = 2975, 2940, 2870, 1469, 1411, 1357, 1116, 1049 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.60 (s, 15H), 1.68 (s, 3H), 1.77 (s, 3H), 1.8–2.2 (m, 20H), 2.14 (s, 3H), 3.32 (d, 2H, J = 6.6 Hz), 3.79 (s, 6H), 3.91 (s, 6H), 5.0–5.5 (m, 6H).

1-[(2*E*,6*E*,10*E*,14*E*,18*E*)-22,23-Epoxy-3,7,11,15,19,23-hexamethyl-2,6,10,14,18-tetracosapentaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (32):

To a solution of **31** (1.10 g, 1.77 mmol) in H_2O (0.04 mL) and THF (4 mL) is added NBS (472 mg, 2.65 mmol) portionwise. After stirring at r.t. for 1 h, H_2O (4 mL) is added. The aqueous layer is extracted with Et_2O (4 mL × 2) and the combined organic layer is dried ($MgSO_4$). Filtration and concentration provides the crude bromohydrin as an oil, which is dissolved in MeOH (4 mL). To this solution is added a solution of MeONa in MeOH (28%, 548 mg, 2.84 mmol) dropwise at 0°C. After stirring at 0°C for 30 min, Et_2O

(10 mL) and H_2O (10 mL) are added. The organic layer is separated, dried ($MgSO_4$), and concentrated. The crude product is chromatographed on silica gel (hexane/Et_2O, 5:1) to give **32** as an oil; yield: 361 mg (32%); R_f 0.52 (hexane/Et_2O, 3:2).

$C_{41}H_{64}O_5$ (637.0) calc. C 77.31 H 10.13 found 77.13 10.10

IR (CCl_4): ν = 2980, 2945, 2875, 1472, 1417, 1117, 1052 cm^{-1}.

^1H-NMR ($CDCl_3$): δ = 1.26 (s, 3H), 1.30 (s, 3H), 1.5–1.7 (m, 2H), 1.59 (s, 6H), 1.61 (s, 6H), 1.77 (s, 3H), 1.8–2.2 (m, 18H), 2.14 (s, 3H), 2.71 (t, 1H, J = 6.5 Hz), 3.32 (d, 2H, J = 6.6 Hz), 3.79 (s, 6H), 3.91 (s, 6H), 5.0–5.2 (m, 5H).

Diisopropyl [(4*E*,8*E*,12*E*,16*E*,20*E*)-1-Isopropenyl-4,8,12,16,20-pentamethyl-22-(2,3,4,5-tetramethoxy-6-methylphenyl)-4,8,12,16,20-docosapentaenyl]phosphate (33):

The phosphate **33** was synthesized from **32** under the conditions described for the formation of **30**; chromatography condition: hexane/Et_2O, 1:2; 80% yield; R_f 0.40 hexane/Et_2O, 1:4).

$C_{47}H_{77}O_8P$ (801.1) calc. C 70.47 H 9.69 found 70.40 9.81

IR (KBr): ν = 2985, 2930, 2855, 1657, 1462, 1409, 1260, 1110, 1000 cm^{-1}.

^1H-NMR ($CDCl_3$): δ = 1.2–1.4 (m, 12H), 1.59 (s, 12H), 1.7–1.9 (m, 2H), 1.73 (s, 3H), 1.77 (s, 3H), 1.9–2.2 (m, 18H), 2.14 (s, 3H), 3.32 (d, 2H, J = 6.6 Hz), 3.79 (s, 6H), 3.91 (s, 6H), 4.4–4.7 (m, 2H), 4.8–4.9 (m, 1H), 4.92 (s, 1H), 5.00 (s, 1H), 5.0–5.2 (m, 5H).

1-[(2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-Decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (34):

The product **34**[30] was synthesized from **33** under the conditions described for the formation of **31**; chromatography condition: hexane/Et_2O, 10:1; yield 96%; R_f 0.33 (hexane/Et_2O, 10:1).

IR (KBr): ν = 2920, 2850, 1672, 1460, 1405, 1382, 1353, 1260, 1200, 1104 cm^{-1}.

^1H-NMR ($CDCl_3$): δ = 1.60 (s, 27H), 1.68 (s, 3H), 1.77 (s, 3H), 1.9–2.2 (m, 36H), 2.14 (s, 3H), 3.32 (d, 2H, J = 6.2 Hz), 3.79 (s, 6H), 3.90 (s, 6H), 5.0–5.2 (m, 10H).

Coenzyme Q_{10} (26):

To a solution of **34** (154 mg, 0.17 mmol) in CH_3CN (0.7 mL) and CH_2Cl_2 (0.7 mL) is added a solution of CAN (290 mg, 0.53 mmol) in 50% aq. CH_3CN (1.4 mL) dropwise over a period of 5 min at 0°C. After stirring for 5 min, H_2O (10 mL) is added and the crude product is extracted with Et_2O (10 mL), washed with 5% aq $NaHCO_3$ (10 mL) and H_2O (10 mL), dried ($MgSO_4$), and concentrated. The resulting oil is chromatographed on silica gel (hexane/Et_2O, 10:1) to give **26** as a yellow solid; yield: 106 mg (72%); R_f 0.32 (hexane/Et_2O, 4:1); mp 46.5–47.0°C (recrystallized twice from EtOH, Lit.[30] mp 47°C).

IR ($CHCl_3$): ν = 2920, 2855, 1655, 1615, 1450, 1385, 1265, 1155 cm^{-1}.

^1H-NMR ($CDCl_3$, 500 MHz): δ = 1.58 (s, 3H), 1.60 (s, 24H), 1.68 (s, 3H), 1.74 (s, 3H), 1.9–2.0 (m, 18H), 2.01 (s, 3H), 2.0–2.1 (m, 18H), 3.18 (d, 2H, J = 7.3 Hz), 3.98 (s, 3H), 4.00 (s, 3H), 4.94 (t, 1H, J = 6.8 Hz), 5.06 (t, 1H, J = 6.8 Hz), 5.11 (t, 8H, J = 6.8 Hz).

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