Grignard Coupling Reactions of (*Z*)-Trisubstituted Allylic Acetates with Retention of the Double Bond Stereo- and Regiochemistry

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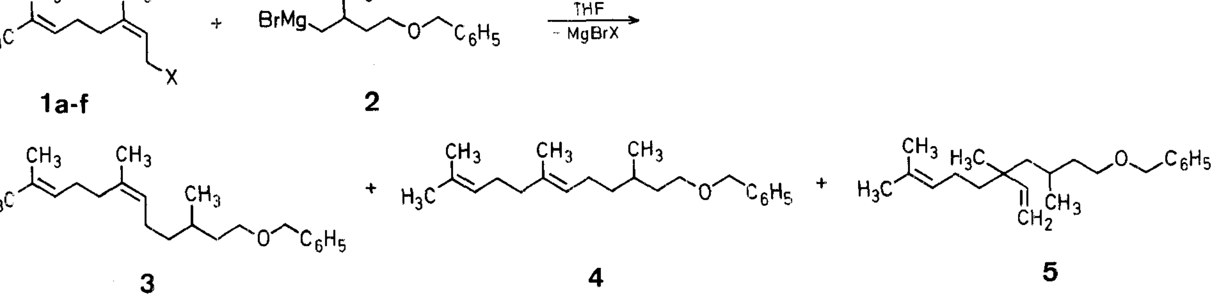
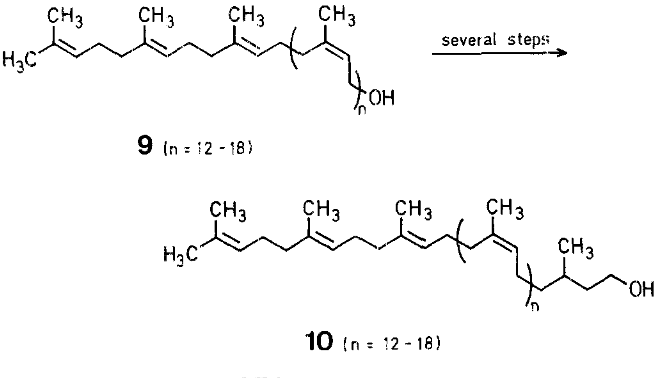
Copper-catalyzed Grignard coupling reactions of allylic compounds are known as useful synthetic tools for stereo- and regioselective carbon-carbon bond formation[1]. However, in the case of allylic substrates having (*Z*)-trisubstituted double bonds, the reaction between 3-ethyl-2(*Z*)-heptenyl ethyl ether and *n*-butylmagnesium chloride is the only example known to proceed with retention of the double bond geometry[2]. We now report that the Grignard coupling reactions of allylic acetates possessing (*Z*)-trisubstituted double bonds can be conducted with retention of the stereo- and regiochemistry.



Several nerol derivatives **1a-f** were reacted with the Grignard reagent **2**, prepared from 4-bromo-3-methylbutyl benzyl ether and magnesium, in the presence of copper salts in order to examine the effect of leaving groups upon the selectivity (Table 1). The reaction of the ether **1a** yielded no coupling product. The bromide **1b**, reported to react with an aromatic Grignard reagent with 88% retention of the double bond geometry[3], and the sulfonium salt **1c** afforded mixtures consisting of the retention product **3**, the stereoisomer **4**, and the regioisomer **5**. The ammonium salt **1d**, the carbonate **1e**, and the acetate **1f** mainly reacted to give products **3** characterized by retention of the double bond geometry. Among these substrates, the acetate **1f** gave the best yield. By using dilithium tetrachlorocuprate instead of copper(I) bromide, the formation of the regioisomer **5** could be suppressed. Furthermore, it was found that the selectivity of the coupling reaction is to some extent dependent on the amount of copper salt used, the reaction temperature, and the solvent (Table 2). The complete preservation of the double bond stereo- and regiochemistry was obtained when the reaction was carried out in the presence of dilithium tetrachlorocuprate (4 mol% related to **1f**) at 0°C in tetrahydrofuran.

Under similar conditions, a variety of acetates possessing (*Z*)-trisubstituted double bonds were reacted with Grignard reagents to give the coupling products **6**, **7**, **8** with retention of the double bond geometry (Table 3).

The present method is useful for the synthesis of various terpenoids having (*Z*)-trisubstituted double bonds. For example, the synthesis of mammalian dolichols (**10**)[4] starting from the polyprenols (**9**), which were isolated from *Ginkgo biloba*, was achieved[5].



3-Methyl-3-butenyl Benzyl Ether:

To a suspension of sodium hydride (50% dispersion in mineral oil, 58.92 g, 1.277 mol) in tetrahydrofuran (500 ml), 3-methyl-3-butenol (100.0 g, 1.161 mol) is added with stirring in 1 h. The mixture is refluxed for 2 h, then after cooling in an ice bath, benzyl chloride (161.7 g, 1.277 mol) is added dropwise. After the mixture has been stirred under reflux for 5 h, it is poured into ice (300 g). The mixture is partitioned between ether (200 ml) and water (300 ml). The ether layer is washed with saturated aqueous sodium chloride (200 ml), dried with magnesium sulfate, concentrated, and distilled under reduced pressure to give 3-methyl-3-butenyl benzyl ether; yield: 113.1 g (55%); b.p. 120–123°C/16 torr.

$C_{12}H_{16}O$	calc.	C 81.78	H 9.15
(176.3)	found	81.60	9.10

I.R. (film): ν = 890, 735, 700 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/HMS): δ = 1.67 (s, 3H); 2.27 (t, J = 6.9 Hz, 2H); 3.50 (t, J = 6.9 Hz, 2H); 4.35 (s, 2H); 4.70 (br. s, 2H); 7.28 ppm (s, 5H).

M.S.: m/e (rel. int.) = 176 (M$^+$, 1); 91 (100).

4-Bromo-3-methylbutyl Benzyl Ether:

To a mixture of sodium borohydride (2.5 g, 0.066 mol) and 3-methyl-3-butenyl benzyl ether (35.2 g, 0.20 mol) in tetrahydrofuran (320 ml) is added at 20°C boron trifluoride etherate (10.1 ml, 0.08 mol) within 10 min. After stirring for 15 min, bromine (13.6 ml, 0.266 mol) is added dropwise at 0°C followed by a 28% solution of sodium methoxide in methanol (64.0 g, 0.33 mol), the temperature being kept below 5°C. Stirring is continued for 20 min at 20°C. The mixture is partitioned between ether (300 ml) and saturated aqueous sodium chloride (500 ml). The ether layer is washed with saturated aqueous sodium chloride

(200 ml), dried with magnesium sulfate, concentrated, and distilled under reduced pressure to give 4-bromo-3-methylbutyl benzyl ether; yield: 38.08 g (75%): b.p. 97–98 °C/0.3 torr.

$C_{12}H_{17}OBr$	calc.	C 56.05	H 6.66
(257.2)	found	56.17	6.69

I.R. (film): $\nu = 735, 695, 650\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$/HMS): $\delta = 1.02$ (d, $J = 6.6$ Hz, 3 H); 1.3–2.3 (m, 3 H); 3.3–3.6 (m, 4 H); 4.49 (s, 2 H); 7.35 ppm (s, 5 H).

M.S.: *m/e* (rel. int.) = 256 (M^+, 0.05); 91 (100).

Table 1. Coupling Reaction of Nerol Derivatives **1** with the Grignard Reagent **2** in Tetrahydrofuran under Argon

Substrate No.	X	Molar Ratio **2** : **1**	Copper Salt (mol% based on **1**)	Reaction Temperature	Yield [%][a]	Product Distribution [%][a]		
						3	**4**	**5**
1a	OCH_3	1.5	CuBr[b] (5)	0 °C	0	—	—	—
1b	Br	1.5	$Li_2[CuCl_4]$ (1.5)	−30 °C	56[c]	33	22	45
1c	$-\overset{\oplus}{S}(CH_3)_2Br^{\ominus}$	2	CuBr (4)	0 °C	66	54	2	44
1d	$-\overset{\oplus}{N}(C_2H_5)_3Br^{\ominus}$	2	CuBr (4)	0 °C	43	98	1	1
1e	$-O-CO-OC_2H_5$	2	CuBr (4)	0 °C	67	98	1	1
1f	$-O-CO-CH_3$	2	CuBr (4)	0 °C	75	95	0	5

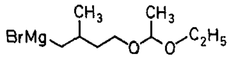
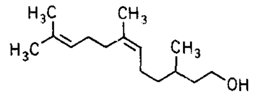
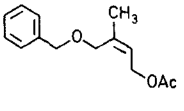
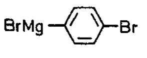
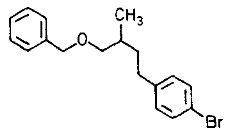
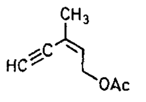
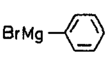
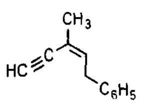
[a] Determined by G.L.C. (2 m column of Silicone GE SE-30, 5% on Chromosorb W, 60–80 mesh).
[b] Triethyl phosphite (15 mol% based on **1a**) also added.
[c] Yield of isolated product.

Table 2. Coupling of Acetate **1f** with Grignard Reagent **2** in the Presence of Dilithium Tetrachlorocuprate; Effect of Reaction Conditions

Molar Ratio of **2**: **1f**	$Li_2[CuCl_4]$ (mol% based on **1f**)	Reaction Temperature	Solvent	Yield [%][a]	Product Distribution [%][a]		
					3	**4**	**5**
1.5	4	0 °C	THF	62	100	0	0
2	16	0 °C	THF	76	91	0	9
1.5	4	+20 °C	THF	74	95	1	4
2	4	0 °C	ether	75	80	0	20

[a] Determined by G.L.C. (2 m column of Silicone GE SE-30, 5% on Chromosorb W, 60–80 mesh).

Table 3. Grignard Coupling Products from (*Z*)-Trisubstituted Allylic Acetates[a]

Allylic Acetate	Grignard Reagent	Product	Yield [%]	b.p. [°C]/torr	Molecular formula[b]
1 (X = OAc) (5 mmol)	**2** (10 mmol)	**3**[c]	79	134°/0.2	$C_{22}H_{34}O$ (314.5)
1 (X = OAc) (5 mmol)	 (10 mmol)	 **6**[c,d]	66	—	$C_{15}H_{28}O$ (224.4)
 (5 mmol)	 (8 mmol)	 **7**[e]	49	—	$C_{18}H_{19}BrO$ (331.3)
 (20 mmol)[f]	 (30 mmol)	 **8**[f]	70	150–170°/20[g]	$C_{12}H_{12}$ (156.2)

[a] Reactions in tetrahydrofuran under argon at 0 °C in the presence of 4 mol% dilithium tetrachlorocuprate.
[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.41.
[c] No isomer was detected by G.L.C. analysis; for **3**: 2 m column of Silicone GE SE-30, 5% on Chromosorb W, 60–80 mesh; for 1-ethoxyethyl ether of **8**: 2 m column of Silicone DC QF-1, 10% on Chromosorb W, 60–80 mesh.
[d] This alcohol **6** was obtained after treatment of the crude coupling product with 1 vol% solution of hydrochloric acid in ethanol.
[e] The homogenity of **7** was confirmed by ^{1}H-N.M.R. analysis.
[f] (*Z*/*E*) = 86 : 14 (G.L.C. analysis: 2 m column of Polyethylene Glycol 20M, 5% on Chromosorb W, 60–80 mesh).
[g] Bath temperature of Kugelrohr distillation apparatus.

Table 4. Spectral Data for the Coupling Products **3**, **6–8**

Product No.	I.R. (film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$)[a] δ [ppm]	M.S. *m/e* (rel. int.)
3	1100, 740, 700	0.81 (d, J=6.0 Hz, 3H); 1.1–1.5 (m, 5H); 1.53 (s, 3H); 1.63 (s, 6H); 2.0 (m, 6H); 3.42 (t, J=6.0 Hz, 2H); 4.41 (s, 2H); 5.05 (m, 1H); 7.27 (s, 5H)	223 ($M^+ - C_6H_5$—CH_2, 0.2), 91 (100), 69 (85), 81 (30)
6	3340	0.83 (d, J=6.0 Hz, 3H); 1.05–1.5 (m, 5H); 1.60 (s, 3H); 1.67 (s, 6H); 1.8–2.1 (m, 6H); 3.62 (t, J=6.0 Hz, 2H); 5.1 (m, 1H)	224 (M^+, 0.3), 69 (100), 41 (60), 81 (42)
7	1070, 730, 700	1.76 (s, 3H); 3.25 (d, J=7.5 Hz, 2H); 4.02 (s, 2H); 4.42 (s, 2H); 5.45 (t, J=7.5 Hz, 1H); 6.9–7.4 (m, 9H)	331 (M^+, 25), 224 (100)[b]
8	740, 700	1.85 (s, 3H); 3.08 (s, 1H); 3.58 (d, J=7.5 Hz, 2H); 5.85 (t, J=7.5 Hz, 1H); 7.25 (s, 5H)	156 (M^+, 67), 141 (100), 51 (45)

[a] Hexamethyldisiloxane as internal standard.

[b] Field desorption M.S.

3,7,11-Trimethyl-6,10(*Z*)-dodecadien-1-yl Benzyl Ether (3); Typical Procedure for the Grignard Coupling Reaction:

A mixture of magnesium (0.255 g, 10.5 mmol) and 1,2-dibromoethane (26 µl, 0.3 mmol) in tetrahydrofuran (10 ml) is heated at reflux. To the activated magnesium is added a solution of 4-bromo-3-methylbutyl benzyl ether (2.57 g, 10 mmol) in tetrahydrofuran (2 ml) at 20°C and the mixture is refluxed for 15 min. The Grignard reagent is added dropwise at 0°C under argon to a mixture of the acetate **1f** (0.98 g, 5 mmol) in tetrahydrofuran (8 ml) and a 0.1 molar solution of dilithium tetrachlorocuprate in tetrahydrofuran (2.0 ml, 0.2 mmol). After stirring for 1 h at 0°C, the mixture is partitioned between ether (50 ml) and saturated aqueous ammonium chloride (50 ml). The ether layer is washed with saturated aqueous ammonium chloride (30 ml), dried with magnesium sulfate, concentrated, and distilled under reduced pressure to give **3**; yield: 1.38 g (79%); b.p. 134°C/0.2 torr. The product is further purified by silica gel column chromatography using hexane/isopropyl ether (5/1) as eluent.

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