Regioselective Borohydride and Grignard Reactions in (*E*)-3-(Arylmethylene)-2-oxotetrahydrofurans[1]

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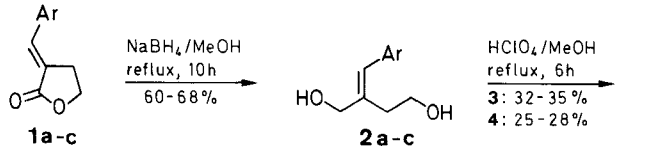
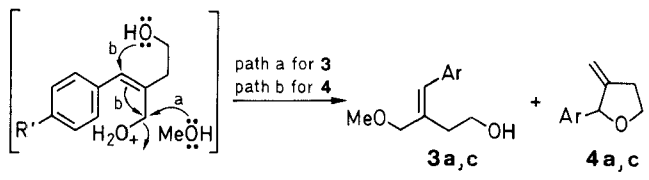
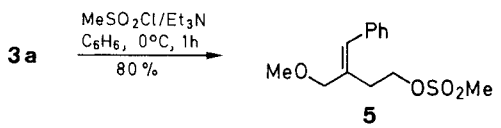
Convenient syntheses of (*E*)-2-(arylmethylene)-1,4-butanediols **2a–c**, 2-(aryl)-3-methylenetetrahydrofurans **4a,c**, 3-(arylmethylene)-2-methyl-2,5-pentanediols **7a–c**, 4-(arylmethylene)-3-ethyl-3,6-hexanediols **7d–f**, 2,2-dialkyl-3-(arylmethylene)tetrahydrofurans **9a–f** and 2,2-dialkyl-3-(arylmethyl)tetrahydrofurans **10a–b, 10d–e** are described. The synthetic utility of the title compounds is obvious from the ease of preparation of these new type of tetrahydrofuran derivatives.

The search for simple synthons capable of furnishing useful intermediates and oxygen heterocycles has revealed the synthetic utility of 3-(arylmethylene)-2-oxotetrahydrofuras. In this paper we describe the hitherto unreported conversion of these compounds into a series of new tetrahydrofuran derivatives.

The syntheses of (*E*)-(arylmethylene)-2-oxotetrahydrofurans **1a–c** and their dihydro analogs **6a–b** were reported earlier.[2] Reduction of **1a–c** with sodium borohydride did not lead to 1,4-addition of hydride. In this reaction the lactone carbonyl alone underwent hydride attack to yield compounds **2a–c**. Treatment of compound **2a** or **2c** with perchloric acid in methanol afforded a mixture of compounds **3a, 4a** or **3c, 4c**, which were separated by column chromatography. Although the synthesis of **4a** has been reported earlier,[3] the present synthesis is more convenient. The structural assignment of **3a** is based on the comparative ^{1}H-NMR studies of **3a** with its mesylated derivative **5a**. The downfield shift of the triplet for OCH_2 protons has helped to ascertain the position of the methoxyl group in **3a**. Unlike **2a** and **2c**, attempted ring closure of **2b** gives polymeric reaction product and no pure compound was isolated from this mixture.

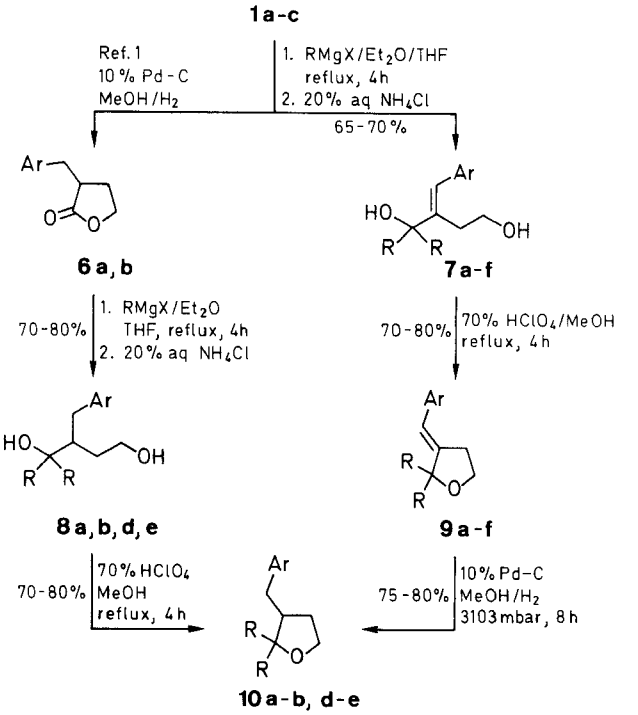






1–4	a	b	c
Ar	Ph	4-$MeOC_6H_4$	4-ClC_6H_4

Reactions of **1a–c** with alkylmagnesium halides yields the diols **7a–f**, which without further purification were cyclized in the presence of perchloric acid in methanol to (*E*)-3-(arylmethylene)-2,2-dialkyltetrahydrofurans **9a–f** (for mechanism see reaction scheme). In order to provide unambiguous support for the assigned structures, compounds, **9a–b, 9d–e** were hydrogenated and the resulting dihydro compounds **10a–b, 10d–e** were compared with those obtained by an alternative route. The first step of the alternate synthesis of **10a–b, 10d–e** involves hydrogenation of **1a–b** to yield **6a–b**.[2] Reaction of these compounds with alkylmagnesium halide gives **8a–b, 8d–e**, which undergo ring closure to furnish **10a–b, 10d–e**, identical in all respects with those obtained from **9a–b, 9d–e**, respectively (Table).



6–10	Ar	R	6–10	Ar	R
a	Ph	Me	**d**	Ph	Et
b	4-$MeOC_6H_4$	Me	**e**	4-$MeOC_6H_4$	Et
c	4-ClC_6H_4	Me	**f**	4-ClC_6H_4	Et

However, the ring opening of **1a–c** by Grignard reaction with alkylmagnesium halide followed by recyclization with perchloric acid furnished **9a–f** as the major product. The Dreiding model of these compounds indicates significant steric hindrance in *Z*-isomers. Based on this consideration, compounds **9a–f** were assigned the *E*-stereochemistry. Stereoselectivity in the formation of the *E*-isomers in structurally related compounds **1a–c** has been described earlier.[4–6]

Table. Compounds **2–5** and **7–10** Prepared

Product	Yield[a] (%)	Molecular Formula[b]	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS m/z (%)
2a	68	$C_{11}H_{14}O_2$ (178.2)	3380, 3370	2.45 (t, 2H, J = 7, H-3), 3.61 (t, 2H, J = 7, CH_2O), 4.40 (s, 2H, H-1), 4.40 (br, s, 2H, OH), 6.44 (s, 1H, =CH), 7.10 (s, 5H$_{arom}$)	178 (M^+, 28), 91 (98)
2b	60	$C_{12}H_{16}O_3$ (208.2)	3380, 3375	2.46 (t, 2H, J = 7, H-3), 3.60 (t, 2H, J = 7, CH_2O), 3.65 (s, 3H, OCH_3), 3.80 (br s, 2H, OH, merged with OCH_3), 4.02 (s, 2H, H-1), 6.39 (s, 1H, =CH), 6.68 (d, 2H$_{arom}$), J = 8), 7.0 (d, 2H$_{arom}$, J = 8)	208 (M^+, 23), 121 (92)
2c	65	$C_{11}H_{13}ClO_2$ (212.7)	3375, 3365	2.44 (t, 2H, J = 7, H-3), 3.63 (t, 2H, J = 7, CH_2O), 3.90 (br s, 2H, OH), 4.05 (s, 2H, H-1), 6.42 (s, 1H, =CH), 7.10 (q, 4H$_{arom}$, J = 8)	212 (M^+, 31), 214 (M^+ + 2, 10), 129 (100)
3a	35	$C_{12}H_{16}O_2$ (192.1)	3380	2.44 (t, 2H, J = 7, H-2), 2.78 (br s, 1H, OH), 3.28 (s, 3H, OCH_3), 3.61 (t, 2H, J = 7, CH_2O), 3.90 (s, 2H, H-4), 6.49 (s, 1H, =CH), 7.15 (s, 5H$_{arom}$)	192 (M^+, 32), 129 (97)
3c	32	$C_{12}H_{15}ClO_2$ (226.5)	3375	2.40 (t, 2H, J = 7, H-2), 2.68 (br s, 1H, OH), 3.28 (s, 3H, OCH_3), 3.60 (t, 2H, J = 7, CH_2O), 3.89 (s, 2H, H-4), 6.42 (s, 1H, =CH), 7.20 (s, 4H$_{arom}$)	226 (M^+, 32), 228 (M^+ + 2, 18), 181 (100)
4a	28	$C_{11}H_{12}O$ (160.2)	–	2.60 (m, 2H, H-4), (m, 2H, CH_2O), 4.61 (t, 1H, J = 1, CHO), 4.95 (m, 2H, =CH_2), 7.20 (s, 5H$_{arom}$)	160 (M^+, 82), 105 (100)
4c[c]	25	$C_{11}H_{11}ClO$ (194.6)	–	2.61 (m, 2H, H-4), 3.95 (m, 2H, CH_2O), 4.62 (t, 1H, J = 1, CHO), 4.94 (m, 2H, =CH_2), 7.28 (s, 4H$_{arom}$)	194 (M^+, 55), 196 (M^+ + 2,39), 139 (100)
5	80	$C_{13}H_{18}SO_4$ (270.2)	–	2.72 (t, 2H, J = 7, H-2), 3.20 (s, 3H, SO_2CH_3), 3.22 (s, 3H, OCH_3), 3.90 (s, 2H, H-4), 4.18 (t, 2H, J = 7, CH_2O), 6.50 (s, 1H, =CH), 7.15 (s, 5H$_{arom}$)	270 (M^+, 7), 129 (100)
7a	75	$C_{13}H_{18}O_2$ (206.2)	3360	1.32 (s, 6H, CH_3), 2.46 (t, 2H, J = 6, H-4), 3.48 (t, 2H, J = 6, CH_2O), 4.6 (br s, 2H, OH), 6.40 (s, 1H, =CH), 7.05 (m, 5H$_{arom}$)	206 (M^+, 24), 189 (100)
7b	70	$C_{14}H_{20}O_3$ (236.3)	3360, 3340	1.29 (s, 6H, CH_3), 2.45 (t, 2H, J = 6, H-4), 3.54 (s, 3H, OCH_3), 3.70 (t, 2H, J = 6, CH_2O), 4.40 (br s, 2H, OH), 5.98 (s, 1H, =CH), 6.65 (d, 2H$_{arom}$, J = 7), 7.0 (d, 2H$_{arom}$, J = 7)	236 (M^+, 8), 203 (100)
7c	72	$C_{13}H_{17}ClO_2$ (240.7)	3360, 3335	1.32 (s, 6H, CH_3), 2.45 (t, 2H, J = 6, H-4), 3.48 (t, 2H, J = 6, CH_2O), 4.82 (br s, 2H, OH), 6.35 (s, 1H, =CH), 7.04 (q, 4H$_{arom}$, J = 8)	240 (M^+, 6), 242 (M^+2, 2), 43 (100)
7d	72	$C_{15}H_{22}O_2$ (234.3)	3410, 3400	0.82 (t, 6H, J = 5, C$\underline{H}_3$CH$_2$), 1.55 (m, 4H, CH$_3$C$\underline{H}_2$), 2.44 (t, 2H, J = 6, H-5), 3.48 (t, 2H, J = 6, CH_2O), 4.65 (br s, 2H, OH), 6.28 (s, 1H, =CH), 7.10 (m, 5H$_{arom}$)	234 (M^+, 5), 205 (99)
7e	65	$C_{16}H_{24}O_3$ (264.3)	3410, 3390	0.85 (t, 6H, J = 5, C$\underline{H}_3$CH$_2$), 1.56 (m, 4H, CH$_3$C$\underline{H}_2$), 2.46 (t, 2H, J = 6, H-5), 3.63 (s, 3H, OCH_3), 3.72 (t, 2H, J = 6, CH_2O), 4.50 (br s, 2H, OH), 5.92 (s, 1H, =CH), 6.55 (d, 2H$_{arom}$, J = 7), 7.0 (d, 2H$_{arom}$, J = 7)	264 (M^+, 3), 217 (91)
7f	68	$C_{15}H_{21}ClO_2$ (268.7)	3400, 3385	0.80 (t, 6H, J = 5, C$\underline{H}_3$CH$_2$), 1.56 (m, 4H, CH$_3$C$\underline{H}_2$), 2.42 (t, 2H, J = 6, H-5), 3.50 (m, 2H, CH_2O), 4.55 (br s, 2H, OH), 6.23 (s, 1H, =CH), 7.08 (m, 4H$_{arom}$)	268 (M^+, 3), 270 (M^+ + 2,1), 57 (76)
8a	80	$C_{13}H_{20}O_2$ (208.2)	3340, 3330	1.18 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.55 (m, 2H, H-4), 1.85 (m, 1H, H-3), 2.89 (m, 2H, ArC$\underline{H}_2$), 3.45 (m, 2H, CH_2O), 4.35 (br s, 2H, OH), 7.12 (s, 5H$_{arom}$)	208 (M^+, 3), 91 (81)
8b	75	$C_{14}H_{22}O_3$ (238.3)	3335, 3330	1.17 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.58 (m, 2H, H-4), 1.90 (m, 1H, H-3), 2.92 (m, 2H, ArC$\underline{H}_2$), 3.40 (m, 2H, CH_2O), 3.70 (s, 3H, OCH_3), 4.40 (br s, 2H, OH), 6.25 (d, 2H$_{arom}$), 4.40 (br s, 2H, OH), 6.25 (d, 2H$_{arom}$, J = 8), 7.12 (d, 2H$_{arom}$, J = 8)	238 (M^+, 3), 203 (98)
8d	78	$C_{15}H_{24}O_2$ (236.3)	3340, 3330	0.84 (m, 6H, C$\underline{H}_3$CH$_2$), 1.48 (m, 6H, CH$_3$C$\underline{H}_2$, H-5), 1.91 (m, 1H, H-4), 2.78 (m, 2H, ArC$\underline{H}_2$), 3.40 (m, 2H, CH_2O), 4.38 (br s, 2H, OH), 7.02 (s, 5H$_{arom}$)	236 (M^+, 4), 91 (83)
8e	70	$C_{16}H_{26}O_3$ (266.3)	3340, 3330	0.84 (m, 6H, C$\underline{H}_3$CH$_2$), 1.58 (m, 6H, CH$_3$C$\underline{H}_2$ + H-5), 1.82 (m, 1H, H-4), 2.82 (m, 2H, ArC$\underline{H}_2$), 3.55 (m, 2H, CH_2O), 3.70 (s, 3H, OCH_3), 4.40 (br s, 2H, OH), 6.75 (d, 2H, J = 8), 7.02 (d, 2H$_{arom}$, J = 8)	266 (M^+, 3), 121 (91)
9a	80	$C_{13}H_{16}O$ (188.2)		1.20 (s, 6H, CH_3), 2.73 (dt, 2H, J = 1.5, 7, H-4), 3.74 (t, 2H, J = 7, CH_2O), 6.0 (t, 1H, J = 1.5, =CH), 7.08 (s, 5H$_{arom}$)	188 (M^+, 20), 173 (100)
9b	75	$C_{14}H_{18}O_2$ (218.2)		1.30 (s, 6H, CH_3), 2.78 (dt, 2H, J = 1.5, 7, H-4), 3.70 (s, 3H, OCH_3), 3.85 (t, 2H, J = 7, CH_2O), 6.05 (t, 1H, J = 1.5, =CH), 6.80 (d, 2H$_{arom}$, J = 8), 7.16 (d, 2H$_{arom}$, J = 8)	218 (M^+, 31), 203 (97)
9c	76	$C_{13}H_{15}ClO$ (222.7)		1.25 (s, 6H, CH_3), 2.71 (dt, 2H, J = 1.5, 7, H-4), 3.78 (t, 2H, J = 7, CH_2O), 5.98 (t, 1H, J = 1.5, =CH), 7.10 (m, 4H$_{arom}$)	222 (M^+, 8), 224 (M^+ + 2, 3), 43 (100)
9d	78	$C_{15}H_{20}O$ (216.3)		0.81 (t, 6H, J = 8, C$\underline{H}_3$CH$_2$), 1.54 (m, 4H, CH$_3$C$\underline{H}_2$), 2.73 (dt, 2H, J = 1.5, 7, H-4), 3.80 (t, 2H, J = 7, CH_2O), 5.98 (t, 1H, J = 1.5, =CH), 7.10 (s, 5H$_{arom}$)	216 (M^+, 7), 187 (100)

Table. (continued)

Product	Yield[a] (%)	Molecular Formula[b]	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)	MS m/z (%)
9e	72	$C_{16}H_{22}O_2$ (246.3)		0.80 (t, 6H, J = 8, CH_3CH_2), 1.60 (m, 4H, CH_3CH_2), 2.75 (dt, 2H, J = 1.5, 7, H-4), 3.70 (s, 3H, OCH_3), 3.86 (t, 2H, J = 7, CH_2O), 5.95 (t, 1H, J = 1.5, =CH), 6.75 (d, $2H_{arom}$, J = 8), 7.14 (d, $2H_{arom}$, J = 8)	246 (M^+, 6), 217 (91)
9f	76	$C_{15}H_{19}ClO$ (250.7)		0.80 (t, 6H, J = 8, CH_3CH_2), 1.54 (m, 4H, CH_3CH_2), 2.70 (dt, 2H, J = 1.5, 7, H-4), 3.80 (t, 2H, J = 7, CH_2O), 6.55 (t, 1H, J = 1.5, =CH), 7.10 (s, $4H_{arom}$)	250 (M^+, 4), 252 (M^+), 221 (91)
10a	80	$C_{13}H_{18}O$ (190.2)		1.0 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.62 (m, 3H, H-3 + H-4), 2.60 (dd, 2H, J = 5, 13, $ArCH_2$), 3.62 (m, 2H, CH_2O), 7.05 (s, $5H_{arom}$)	190 (M^+, 21), 91 (82)
10b[d]	78	$C_{14}H_{20}O_2$ (220.3)		1.05 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.60 (m, 3H, H-3 + H-4), 2.62 (dd, 2H, J = 5, 13, $ArCH_2$), 3.64 (m, 2H, CH_2O), 3.68 (s, 3H, OCH_3), 6.74 (d, $2H_{arom}$, J = 8), 7.0 (d, $2H_{arom}$, J = 8)	220 (M^+, 12), 121 (100)
10d	80	$C_{15}H_{22}O$ (218.3)		0.87 (t, 6H, J = 7, CH_3CH_2), 1.46 (m, 6H, H-4 + CH_3CH_2), 1.80 (m, 1H, H-3), 2.68 (dd, 2H, J = 5, 13, $ArCH_2$), 3.60 (m, 2H, CH_2O), 7.05 (s, $5H_{arom}$)	218 (M^+, 20), 189 (91)
10e	76	$C_{16}H_{24}O_2$ (248.3)		0.85 (t, 6H, J = 7, CH_3CH_2), 1.42 (m, 6H, H-4 + CH_3CH_2), 1.76 (m, 1H, H-3), 2.60 (dd, 2H, J = 5, 13, $ArCH_2$), 3.55 (m, 2H, CH_2O), 3.68 (s, 3H, OCH_3), 6.58 (d, $2H_{arom}$, J = 8), 6.89 (d, $2H_{arom}$, J = 8)	248 (M^+, 20), 121 (100)

[a] Yield of pure isolated products. All products were obtained as oils.
[b] Satisfactory microanalyses obtained: C ±0.31, H ±0.25.
[c] ^{13}C-NMR ($CDCl_3$/TMS): δ = 33.07 (t, CH_2), 67.39 (t, CH_2O), 82.27 (d, CHO), 107.25 (t, $=CH_2$), 128.32, 128.47 (2d, CH_{arom}), 133.49, 140.11 (2s, C_{arom}), 151.12 (s, $CH_2=C$).
[d] ^{13}C-NMR ($CDCl_3$/TMS): δ = 21.98 (q, CH_3), 27.49 (q, CH_3), 31.77 (t, CH_2), 35.59 (t, $ArCH_2$), 54.44 (d, CH), 54.95 (q, OCH_3), 64.52 (t, CH_2O), 81.21 (s, OC), 113.66 (d, CH_{arom}), 129.28 (d, CH_{arom}), 132.94 (s, C_{arom}), 157.79 (s, C_{arom}).

The following instruments were used for recording the spectra. IR: Beckman-Acculab-1 spectrophotometer, ^{1}H-NMR: Perkin-Elmer R-32 90 MHz spectrometer, ^{13}C-NMR: Bruker WM 400 MHz spectrometer. MS: Jeol JMS D-300 mass spectrometer (70 eV).

(*E*)-2-(Arylmethylene)-1,4-butanediols 2a–c; General Procedure:
To a stirred solution of **1** (4 mmol) in MeOH (8 mL) is added $NaBH_4$ (1.5 g, 38 mmol) at 5 °C and the mixture is refluxed for 8 h. After cooling, it is neutralized with cold 2 N HCl and extracted with $CHCl_3$ (3 × 60 mL). The combined organic extracts are washed with brine (60 mL), water (2 × 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the oily diols **2** (Table).

(*E*)-3-(Arylmethylene)-4-methoxy-1-butanols 3a,3c and 2-(Aryl)-3-methylenetetrahydrofurans 4a,4c; General Procedure:
To a stirred solution of **2** (3.5 mmol) in MeOH (8 mL) is added slowly 70% $HClO_4$ (0.6 mL) and the mixture is refluxed for 1.5 h. Excess of MeOH is evaporated, the residue diluted with water (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts are washed successively with 5% $NaHCO_3$ solution (50 mL), 20% NaCl solution (50 mL), water (2 × 50 mL), and dried (Na_2SO_4). The solvent is evaporated and the residue is subjected to chromatography on a silica gel column (20 cm × 2 cm, 60–120 mesh). Elution with benzene/hexane (9:1) affords pure **4a,4c** as oils. Further elution with EtOAc/benzene (5:2) affords pure **3a, 3c** as oils (Table).

3-(Arylmethylene)-2-methyl-2,5-pentanediols 7a–c; 4-(Arylmethylene)-3-ethyl-3,6-hexanediols 7d–f, 3-(Arylmethyl)-2-methyl-2,5-pentanediols 8a–b, 4-(Arylmethyl)-3-ethyl-3,6-hexanediols 8d–e; General Procedure:
A solution of alkylmagnesium halide is prepared from alkyl halide (90 mmol) and magnesium (2.16 g, 19 mmol) in anhydrous Et_2O (60 mL). A solution of **1** or **6** (3 mmol) in dry THF (60 mL) is slowly added to the Grignard reagent under stirring and then the mixture is refluxed for 4 h. After cooling, 20% NH_4Cl solution (100 mL) is added slowly and the mixture is stirred for 30 min. The organic product is extracted with $CHCl_3$ (3 × 80 mL) and the combined organic extracts are washed with water and dried (Na_2SO_4). Evaporation of the solvent furnishes crude diols **7** and **8** as oils (Table).

(*E*)-2,2-Dialkyl-3-(arylmethylene)tetrahydrofurans 9a–f and 2,2-Dialkyl-3-(arylmethyl)tetrahydrofurans 10a–b, 10d–e; General Procedure:
To a stirred solution of **7** or **8** (6 mmol) in MeOH (10 mL) is added slowly 70% $HClO_4$ (1 mL) and the mixture is refluxed for 2 h. Excess of MeOH is evaporated, the residue diluted with water (100 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts are washed with water, dried (Na_2SO_4) and evaporated. The residue is purified by filtration through a column of Florisil (20 g, benzene/$CHCl_3$, 1:1. Evaporation of the solvent furnishes pure **9** and **10** as pure oils (Table).

Conversion of 9a to 10a; Typical Procedure:
A mixture of 10% Pd–C (200 mg) and 8a (800 mg, 4 mmol) in MeOH (15 mL) is subjected to hydrogenation (3103 mbar, 25 °C) for 6 h. The catalyst is filtered and the solvent is evaporated. The crude residue is purified by filtration through Florisil (15 g, benzene/$CHCl_3$; 2:1). Evaporation of solvent furnishes pure **10a** as oil; yield: 670 mg (80%).

1-Mesyloxy-4-methoxy-3-(phenylmethylene)butane (5); Typical Procedure:
To a stirred solution of **3a** (270 mg, 1 mmol) in anhydrous benzene (5 mL) is added successively mesyl chloride (0.1 mL, 1.2 mmol) and Et_3N (0.2 mL, 1.5 mmol) and stirring is continued for 1.5 h at 5–10 °C. The mixture is quenched with water (50 mL) and extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts are washed with 5% $NaHCO_3$ (60 mL), water (2 × 60 mL), and dried (Na_2SO_4). The solvent is evaporated and purified by filtration through a band of Florisil (15 g, benzene) to afford pure **5** as pure oil; yield: 300 mg (80%).

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