Tetrahedron Vol 47, No 35, pp 7471-7476, 1991
Printed in Great Britain

0040-4020/91 $3 00+ 00

Stereoselective Two-Step Chemical Preparation of 1,4-Dialkyl-1,4-dimethoxycyclohexa-2,5-dienes

Francisco Alonso and Miguel Yus*

Departamento de Química Orgánica, Universidad de Alicante,
Aptdo 99, 03080 Alicante, Spain

(*Received in UK* 7 *June* 1991)

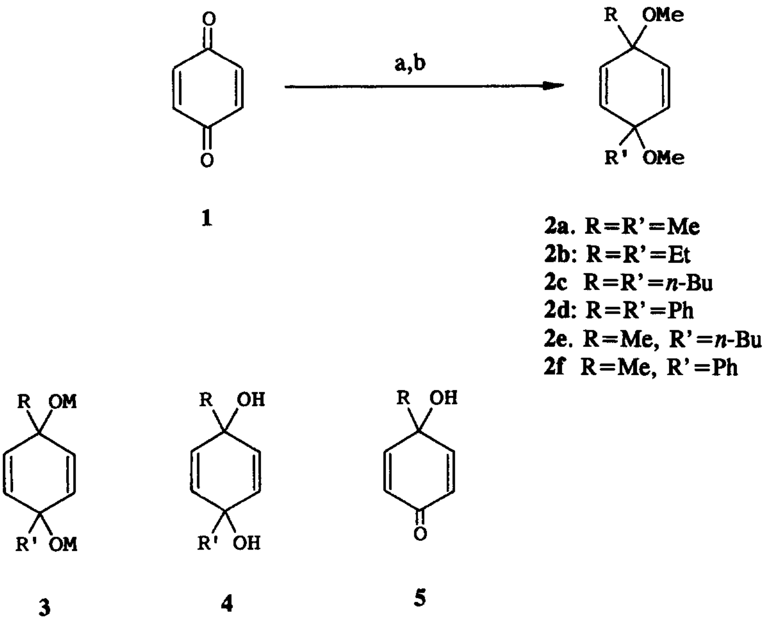
Abstract The reaction of p-benzoquinone (1) with several organolithium compounds (methyl-, ethyl-, n-butyl-, phenyllithium) led, after hydrolysis with water, to the corresponding crude diols ***4****, which were successively treated with sodium hydride and methyl iodide yielding the expected 1,4-dialkyl-1,4-dimethoxycyclohexa-2,5-dienes* ***2a-d*** *in a stereoselective manner The use of a tandem process with two different organolithium reagents followed by methylation by the same procedure yielded stereoselectively the mixed 1-alkyl-4-alkyl' derivatives* ***2e,f***

Introduction

Recently the preparation of 1,4-dimethoxy-1,4-dimethylcyclohexa-2,5-diene (**2a**) has been reported in about 20% yield as a *ca* 1 1 mixture of *cis*/*trans*-diastereomers by electrochemical anodic oxidation of *p*-xylene in methanol-sodium methoxide [1] This compound, which is a versatile precursor in nucleophilic aromatic substitution reactions,[2] has been prepared only by the electrochemical route In this paper we describe the chemical preparation of several compounds of this family starting from *p*-benzoquinone and organolithium compounds, followed by methylation with methyl iodide.

Results and Discussion

We first studied the reaction of *p*-benzoquinone (**1**) with methyllithium[3] (1 3 molar ratio) followed by *in situ* treatment of the dianion **3a** (R=R'=Me, M=Li) with methyl iodide Under these conditions an intractable mixture of products was obtained However, when the methylation was carried out on the corresponding sodium salt **3a** (R=R'=Me, M=Na) the expected product **2a** was isolated *exclusively as the* *cis-diastereomer*. Thus, once the addition of methyllithium took place under the above described conditions the mixture was hydrolyzed with water and extracted. The crude diol **4a** was then treated successively with sodium hydride (1·5 molar ratio) and methyl iodide (1:5 molar ratio) to give *cis*-**2a** in 58% overall isolated yield after flash chromatography (Scheme 1 and Table 1, entry 1). The stereochemistry of **2a** was unequivocally established by comparison of its spectral data with the literature ones.[4] The observed stereochemistry in **2a** is generated in the first step and is due to the electrical repulsion when the second molecule of methyllithium adds to the carbonyl group of the monoaddition adduct from the opposite side of the ring to the OLi group initially formed.[3b] The use of methyllithium containing lithium bromide (30% overall yield) does not alter the observed stereochemistry.



2a. R=R'=Me
2b: R=R'=Et
2c R=R'=*n*-Bu
2d: R=R'=Ph
2e. R=Me, R'=*n*-Bu
2f R=Me, R'=Ph

Scheme 1 *Reagents*. (a) RLi (1·3 molar ratio), then H_2O and extractive workup, for **2a-d**, or (i), RLi (1·1 molar ratio), then H_2O and extractive workup; (ii) R'Li (1:2 molar ratio), then H_2O and extractive workup, for **2e,f**, (b) NaH, then MeI.

When the same reaction was performed with other organolithium reagents such as ethyl, *n*-butyl, or phenyllithium the expected products **2b-d** were isolated in 45-60 overall yield (after flash chromatography) as a mixture of *cis/trans*-diastereomers, the *cis* isomer being the major one in each case. Stereochemical assignments were made by comparing the spectral data of **2b-d** with those of **2a**, for **2b** and **2c** the *cis* isomer is the most polar in chromatography giving the lowest R_f values (Table 1, entries 2 and 3). Both *cis/trans*-**2b,c** have been separated by flash chromatography Alternatively, the intermediate alcohols **4b,c** were separated chromatographically, after the first step, and individually methylated by the mentioned method (Table 1, footnote b). In the case of **2d** the mixture could not be separated by chromatography and it was analyzed by tandem g l c/mass spectrometry. When *sec*- or *tert*-butyllithium were used under the same conditions as for **2a-d** the reaction failed, yielding a mixture of hydroquinone and the corresponding 2-alkylhydroquinone as the only isolated products

Table 1 Preparation of Compounds **2**

Entry	Product 2[a]		
	no	yield (%)[b]	*cis*/*trans*-ratio[c] (R_f)[d]
1	**2a**	58 (83)	100 (0 52)/0
2	**2b**	60 (90)	80 (0.50)/20 (0 53)
3	**2c**	57 (91)	85 (0 47)/15 (0 53)
4	**2d**	45 (72)	75 (0 67)[e,f]/25 (0 67)[e,f]
5	**2e**	28 (88)	91 (0 43)/9 (0 47)
6	**2f**	31 (91)	87 (0 57)[f]/13 (0.59)[f]

[a] All products **2** were >95% pure (g l c and 300 Mhz ^{1}H n m.r.). [b] Isolated overall yield after flash chromatography based on the starting benzoquinone **1**, in parenthesis isolated yield after flash chromatography based on the intermediate alcohols **4** [c] Deduced by g l c. and 300 Mhz ^{1}H n m.r.[d] Silica gel, hexane/ethyl acetate 9/1 [e] *cis*- and *trans*-**2d** could not be separated by t l c.[f] Silica gel, hexane/ethyl acetate 8/2

We also tried to prepare compounds of the type **2** with two different substituents by using two different organolithium reagents before the methylation step Thus, the addition of methyllithium to benzoquinone (1 1 molar ratio) followed by hydrolysis with water and extractive workup gave the expected crude monoaddition product **5** (R=Me), which was treated with butyllithium under the same conditions giving the mixed diol **4** [5] The last methylation yielded the expected product **2e** The same tandem process with phenyl and methyllithium gave the corresponding product **2f** (Table 1, entries 5 and 6) It is noteworthy that also for compounds **2e,f** the process is very stereoselective, the *cis*-isomer being the major one. As for **2b,c** both *cis*/*trans*-**2e,f** have been separated by flash chromatography and the stereochemistry assigned by comparison to the other products **2**, the observed R_f values for **2e,f** are in agreement with the expected polarity for *cis*-

and *trans*-stereochemistry (Table 1, entries 5 and 6).

Finally, we tried to use organomagnesium compounds in the first step of the process instead of the corresponding organolithium intermediates. The reaction led to a mixture of products derived from both 1,2- and 1,4-addition to the starting *p*-benzoquinone, even in the presence of cerium trichloride.[6]

We conclude that this procedure represents the most convenient one to prepare compounds of the type **2**.

Experimental

General.- M.p.s are uncorrected and were measured on a Reichert thermovar apparatus. I.r. spectra were determined with a Pye Unicam SP3-200 spectrometer. ^1H and ^{13}C n.m.r. spectra were recorded on a Bruker AC-300 spectrometer with $SiMe_4$ as internal standard and using $CDCl_3$ as solvent, chemical shifts are given in δ (ppm) and the coupling constants are measured in Hz. M.s. (e.i.) were recorded with a Hewlett Packard EM/CG HP-5988A spectrometer. High resolution mass spectra were obtained with a KRATOS MS 80 RFA spectrometer. The purity of products **2** and the chromatographic analyses (g.l.c.) were determined with a Hewlett Packard HP-5890 instrument equipped with a 12 m WCOT capillary column (0.22 mm diam., 0.2 μm film thickness OV-101 stationary phase) using nitrogen (2 ml/min) as the carrier gas, $T_{injector}$=270°C, T_{column}=60°C (3 min), and 60-270°C (10°C/min), retention times (t_r) are given under these conditions. Thin layer chromatography (t.l.c.) was carried out on aluminum backed plates coated with a 0.2 mm layer of silica gel 60H, using a mixture of hexane/ethyl acetate (9/1 or 8/2, see Table 1) as eluant, R_f values are given under these conditions. Starting materials including organolithium reagents were commercially available (Aldrich) except ethyllithium, which was prepared according to the literature method.[7] Solvents were dried as usually.

Preparation of Compounds **2**. *General Procedure* - To a solution of *p*-benzoquinone (**1**) (0.50 g, 4.6 mmol) in THF (25 ml) was slowly added the corresponding organolithium reagent (13.8 mmol) at -78°C. The resulting solution was stirred for 6 h allowing the temperature to rise to 20°C. The resulting mixture was then hydrolyzed with water (25 ml), extracted with ether (3x30 ml), and the organic layer dried over sodium sulfate. The resulting crude diol **4** was then dissolved in THF (5 ml) and the solution added to a suspension of sodium hydride (*ca.* 25 mmol) in THF (10 ml) at 0°C. After 10 min stirring methyl iodide (*ca.* 25 mmol) was added to the resulting mixture at room temperature and was stirred overnight. The mixture was then hydrolyzed with water (10 ml), extracted with ether (3x10 ml), and the organic layer dried over sodium sulfate. Solvents were evaporated (15 torr) and the residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 98/2) yielding the corresponding compounds **2a-d**.

In the case of mixed compounds **2e,f**, after the first addition of the corresponding organolithium reagent (4.6 mmol, 1.1 molar ratio) and the subsequent hydrolysis as above, the process was repeated with a second organolithium reagent (9.2 mmol, 1.2 molar ratio), and hydrolyzed again. The final methylation and workup as above yielded products **2e,f**.

cis-*3,6-Dimethoxy-3,6-dimethylcyclohexa-1,4-diene* (*cis*-**2a**)[1] t_r=7.60 min, m.p. 64°C (hexane), ν_{max} (KBr) 3040 (HC=C) and 1100 cm^{-1} (C-O), δ_H 1.25 (6 H, s, 2xCMe), 3.18 (6 H, s, 2xOMe), and 5.82 (4 H, s, olefinic H), δ_C 28.5 (2xC*Me*), 52.2 (2xOMe), 71.0 (2xCMe), and 134.1 (olefinic C), *m/z* 168 (M^+, 0.4%), 153 (100), 137 (93), 122 (83), 105 (23), 91 (50), 65 (15), 51 (15), and 43 (17).

cis-*3,6-Diethyl-3,6-dimethoxycyclohexa-1,4-diene* (*cis*-**2b**) t_r=11.24 min, ν_{max} (film) 3010 (HC=C) and 1100 cm^{-1} (C-O), δ_H 0.85 (6 H, t, *J*=7.5, 2xCH$_2$*Me*), 1.57 (4 H, q, *J*=7.5, 2xCH$_2$), 3.19 (6 H, s, 2xOMe), and 5.83 (4 H, s, olefinic H); δ_C 7.9 (2xCH$_2$*Me*), 34.0 (2xCH$_2$), 51.8 (2xOMe), 73.9 (2xCOMe), and 133.9 (olefinic C), *m/z* 168 (M^+-28, 10%), 167 (100), 139 (78), 138 (27), 137 (12), 124 (28), 123 (18), 121 (25), 109 (22), 91 (19), 77 (21), and 65 (10) (Found M$^+$, 196.1441. $C_{12}H_{20}O_2$ requires M, 196.1463).

trans-*3,6-Diethyl-3,6-dimethoxycyclohexa-1,4-diene* (*trans*-**2b**): t_r=11.30 min; ν_{max} (film) 3010 (HC=C) and 1090 cm^{-1} (C-O), δ_H 0 91 (6 H, t, *J*=7 5, 2xCH$_2$*Me*), 1.65 (4 H, q, *J*=7 5, 2xCH$_2$), 3 08 (6 H, s, 2xOMe), and 5.81 (4 H, s, olefinic H); δ_C 8.3 (2xCH$_2$*Me*), 33.8 (2xCH$_2$), 51.6 (2xOMe), 74 0 (2x*C*OMe), and 134.4 (olefinic C); *m/z* 181 (M$^+$-15, 0 1%), 167 (100), 139 (63), 138 (26), 137 (10), 124 (23), 123 (17), 121 (12), 109 (18), 91 (15), and 77 (15) (Found· M$^+$, 196.1475 $C_{12}H_{20}O_2$ requires M, 196 1463).

cis-*3,6-Dibutyl-3,6-dimethoxycyclohexa-1,4-diene* (*cis*-**2c**) t_r=15 71 min; ν_{max} (film) 3010 (HC=C) and 1100 cm^{-1} (C-O), δ_H 0.80 (6 H, t, *J*=6 6, 2xCH$_2$*Me*), 1.17-1 22 (8 H, m, 2xC*H$_2$*C*H$_2$*Me), 1 44-1.49 (4 H, m, 2xC*H$_2$*COMe), 3.11 (6 H, s, 2xOMe), and 5 75 (4 H, s, olefinic H); δ_C 13.9 (2xCH$_2$*Me*), 23.1 (2x*C*H$_2$Me), 25.8 (2x*C*H$_2$CH$_2$Me), 41 3 (2x*C*H$_2$COMe), 51 8 (2xOMe), 73 7 (2x*C*OMe), and 134.0 (olefinic C), *m/z* 221 (M$^+$-31, 0 4%), 195 (76), 139 (100), 124 (59), 123 (17), 121 (57), 109 (10), 91 (28), 78 (14), 77 (20), 57 (12), and 41 (22) (Found M$^+$, 252 1949 $C_{16}H_{28}O_2$ requires M, 252 2089)

trans-*3,6-Dibutyl-3,6-dimethoxycyclohexa-1,4-diene* (*trans*-**2c**) t_r=15 98 min, ν_{max} (film) 3010 (HC=C), 1100, and 1065 cm^{-1} (C-O); δ_H 0 87 (6 H, t, *J*=6 8, 2x CH$_2$*Me*), 1.27-1 33 (8 H, m, 2xC*H$_2$*C*H$_2$*Me), 1 57-1 65 (4 H, m, 2xC*H$_2$*COMe), 3 07 (6 H, s, 2xOMe), and 5 81 (4 H, s, olefinic H), δ_C 13 9 (2xCH$_2$*Me*), 23 2 (2x*C*H$_2$Me), 26.0 (2x*C*H$_2$CH$_2$Me), 41 0 (2x*C*H$_2$COMe), 51 6 (2xOMe), 73.7 (2x*C*OMe), and 134 4 (olefinic C), *m/z* 221 (M$^+$-31, 1%), 196 (11), 195 (83), 139 (100), 138 (22), 124 (63), 123 (36), 121 (45), 109 (12), 95 (10), 91 (35), 77 (20), 57 (12), and 41 (33) (Found M$^+$, 252 2014 $C_{16}H_{28}O_2$ requires M, 252.2089).

cis/trans-*3,6-Dimethoxy-3,6-diphenylcyclohexa-1,4-diene* (*cis*/*trans*-**2d**) t_r=21 94 min (*cis*-isomer) and t_r=22 99 min (*trans*-isomer), m p 124-7°C (hexane), ν_{max} (KBr) 3050, 3010 (HC=C), and 1070 cm^{-1} (C-O), $_H$ 3 43 (6 H, s, 2xOMe), 6 11 (4 H, s, olefinic H), 7 24-7 32, and 7 37-7.42 (10 H, 2 m, ArH); δ_C 51 9 (2xOMe), 74.8 (2x*C*OMe), 133 3 (olefinic C), 126 0, 127.5, 128.3, and 143 4 (ArC), tandem g.l c -*m/z*, *cis*-isomer 293 (M$^+$+1, 15%), 292 (M$^+$, 71), 261 (100), 247 (15), 246 (69), 245 (13), 231 (13), 230 (52), 229 (35), 228 (42), 227 (19), 226 (16), 217 (15), 216 (14), 215 (59), 203 (10), 202 (30), 201 (11), 200 (28), 184 (11), 169 (14), 168 (10), 152 (20), 151 (20), 141 (24), 139 (16), 128 (12), 121 (54), 115 (50), 105 (56), 91 (12), 77 (50), 75 (14), and 51 (24), *trans*-isomer 292 (M$^+$, 0 3%), 261 (21), 260 (100), 245 (17), 227 (27), 226 (17), 215 (18), and 202 (14)

cis-*3-Butyl-3,6-dimethoxy-6-methylcyclohexa-1,4-diene* (*cis*-**2e**)·^{3d} t_r=12 18 min; ν_{max} (film) 3020 (HC=C) and 1090 cm^{-1} (C-O), δ_H 0 86 (3 H, t, *J*=7 2, CH$_2$*Me*), 1 15-1 18 (2 H, m, C*H$_2$*Me), 1 26-1.31 (2 H, m, C*H$_2$*CH$_2$Me), 1 26 (3 H, s, OCMe), 1 52-1 57 (2 H, m, OCCH$_2$), 3 18, 3 19 (6 H, 2 s, 2xOMe), 5 74, and 5 87 (4 H, 2 d, *J*=10 3, olefinic H), δ_C 13 9 (CH$_2$*Me*), 22.9 (*C*H$_2$Me), 26 0 (*C*H$_2$CH$_2$Me), 28 4 (OC*Me*), 40 7 (OC*C*H$_2$), 51 8, 52 1 (2xOMe), 71 1, 74 1 (2x*C*OMe), 132 0, and 135 1 (olefinic C); *m/z* 210 (M$^+$, 0 1%), 154 (14), 153 (100), 138 (27), 123 (32), 122 (22), 121 (18), 105 (15), 91 (22), 79 (13), 77 (26), and 41 (19) (Found M$^+$, 210 1612. $C_{13}H_{22}O_2$ requires M, 210 1620).

trans-*3-Butyl-3,6-dimethoxy-6-methylcyclohexa-1,4-diene* (*trans*-**2e**) ^{3d} t_r=12 14 min, ν_{max} (film) 3020 (HC=C), 1080, and 1070 cm^{-1} (C-O), δ_H 0 87 (3 H, t, *J*=6 6, CH$_2$*Me*), 1 26-1 30 (4 H, m, C*H$_2$*C*H$_2$*Me), 1 31 (3 H, s, OCMe), 1 57-1 63 (2 H, m, OCCH$_2$), 3 04, 3 09 (6 H, 2 s, 2xOMe), 5.70, and 5.86 (4 H, 2 d, *J*=10 4, olefinic H), δ_C 14 0 (CH$_2$*Me*), 23 1 (*C*H$_2$Me), 26 2 (*C*H$_2$CH$_2$Me), 27 7 (OC*Me*), 40.7 (OC*C*H$_2$), 51 1, 52 0 (2xOMe), 71 3, 73 8 (2x*C*OMe), 133 0, and 135 8 (olefinic C), *m/z* 195 (M$^+$-15, 3%), 154 (11), 153 (100), 138 (32), 123 (50), 122 (29), 121 (31), 108 (11), 107 (19), 105 (21), 103 (12), 95 (14), 92 (10), 91 (48), 79 (29), 78 (22), 77 (53), 65 (16), 53 (10), 51 (12), 43 (15), and 41 (61)

cis-*3,6-Dimethoxy-3-methyl-6-phenylcyclohexa-1,4-diene* (*cis*-**2f**) ^{8} t_r=15 85 min; ν_{max} (film) 3050, 3015 (HC=C), 1090, 1070 cm^{-1} (C-O), δ_H 1 35 (3 H, s, OCMe), 3.26, 3.38 (6 H, 2 s, 2xOMe), 5.92, 5 97 (4 H, 2 d, *J*=10 5, olefinic H), 7 25 (1 H, d, *J*=7.0, *p*-ArH), 7.32 (2 H, t, *J*=7 4, 2x*m*-ArH), and 7.41 (2 H, d, *J*=7 2, 2x*o*-ArH), δ_C 28.1 (OC*Me*), 51 8, 52 3 (2xOMe), 70 9 (*C*Me), 75 0 (*C*Ph), 133.2, 134 4 (olefinic C), 125 7, 127 3, 128 4, and 143 8 (ArC), *m/z* 231 (M$^+$+1, 7%), 230 (M$^+$, 45), 216 (11), 215 (74), 200 (58), 199 (100), 198 (11), 185 (23), 184 (91), 183 (22), 173 (15), 172 (24), 169 (22), 168 (40), 167 (47), 166 (20), 165 (51), 155 (19), 154 (16), 153 (60), 152 (57), 151 (10), 141 (45), 139 (27), 138 (17), 129 (18), 128 (33), 127 (14), 123 (14), 122 (10), 121 (13), 115 (71), 105 (12), 102 (12), 91 (27), 89 (23), 79 (10), 78 (18), 77 (71), 76 (10), 75 (15), 65 (13), 63 (20), 59 (17), 51 (39), and 43 (16)

trans-*3,6-Dimethoxy-3-methyl-6-phenylcyclohexa-1,4-diene* (*trans*-**2f**) [8] t_r=15.78 min; ν_{max} (film) 3050, 3010 (HC=C), 1080, and 1070 cm^{-1} (C-O); δ_H 1.39 (3 H, s, OCMe), 3 17, 3.24 (6 H, 2 s, 2xOMe), 5.88, 5.99 (4 H, 2 d, *J*=10.4, olefinic H), 7.27 (1 H, d, *J*=5 1, *p*-ArH), 7.33 (2 H, t, *J*=7 3, 2x*m*-ArH), and 7.51 (2 H, d, *J*=7.2, 2x*o*-ArH); δ_C 27.7 (OC*Me*), 51.2, 52.3 (2xOMe), 70.8 (*C*Me), 74 9 (*C*Ph), 132.9, 135 4 (olefinic C), 125.8, 127.4, 128.3, and 144 1 (ArC); *m/z* 231 (M^++1, 10%), 230 (M^+, 64), 215 (60), 200 (56), 199 (100), 198 (10), 185 (22), 184 (92), 183 (21), 173 (21), 172 (25), 169 (22), 168 (36), 167 (49), 166 (20), 165 (53), 155 (19), 154 (14), 153 (60), 152 (60), 151 (10), 141 (41), 139 (24), 138 (17), 129 (16), 128 (30), 127 (14), 123 (14), 121 (11), 115 (59), 105 (12), 102 (10), 91 (23), 89 (22), 78 (12), 77 (53), 76 (10), 75 (14), 65 (12), 63 (18), 59 (23), 51 (28), 50 (10), and 43 (16)

Acknowledgements

We thank DGICYT (no. PB88-0287) and Lilly S A for financial support. We also thank Dr J M Vega, University of Sevilla for HRMS determinations.

References and notes

1 Barba, F.; Guirado, A , Barba, I. *J Org Chem* **1984**, *49*, 3022

2 (a) Alonso, F ; Barba, I , Yus, M. *Tetrahedron* **1990**, *46*, 2069 (b) Alonso, F ; Yus, M *Ibid* , **1991**, *47*, 313.

3. For general and recent reports on the reaction of quinones and related systems with organolithium reagents see, for instance. (a) Ulrich, H; Richter, R. In *Methoden der Organischen Chemie* (Houben-Weyl), George Thieme Verlag. Stuttgart, 1977, Vol. 7/3A, pp 698-700 (b) Fischer, A ; Henderson, G N. *Tetrahedron Lett.* **1980**, 701. (c) Liotta, D ; Saindane, M ; Barnum, C. *J. Org. Chem.* **1981**, *46*, 3369 (d) Solomon, M , Jamison, W C L.; McCormick, M , Liotta, D , Cherry, D A , Mills, J E.; Shah, R D.; Rodgers, J. D., Maryanoff, C A *J Am Chem. Soc* **1988**, *110*, 3703 (e) Stern, A. J., Rohde, J. J.; Swenton, J S *J. Org. Chem.* **1989**, *54*, 4413 (f) Doty, B J., Morrow, G W *Tetrahedron Lett.* **1990**, *31*, 6125 (g) Swiss, K. A ; Liotta, D C , Maryanoff, C A *J Am Chem Soc* **1990**, *112*, 9393

4 Barba, I ; Alonso, F.; Florencio, F *J Org. Chem.* **1989**, *54*, 4365

5. We thank I Micó for carrying out this experiment.

6 Innamoto, T , Takiyama, N , Nakamura, K , Hatajima, T , Kamiya, Y *J Am Chem Soc* **1989**, *111*, 4392

7 Wakefield, B J. *Organolithium Methods*, Academic Press London, 1988, p 24.

8 Barba, I., Chinchilla, R , Gómez, C *Tetrahedron* **1990**, *46*, 7813