

Tetrahedron 54 (1998) 12389-12398

TETRAHEDRON

Metalation of Arylmethyl Alkyl Ethers

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Received 19 May 1998; revised 28 July 1998; accepted 5 August 1998

Abstract. Arylmethyl alkyl ethers 1a-11 were metallated with *n*-BuLi or *sec*-BuLi in THF at different temperatures, affording α -alkoxy-substituted arylmethyllithium derivatives. At low temperature, the organometallics derived from methyl and isopropyl ethers are sufficiently stable to react with added electrophiles affording the expected products 4aa-4jb. On the contrary, under similar conditions, lithium derivatives of primary alkyl benzyl ethers rapidly decay to benzyl alcohol 3. © 1998 Elsevier Science Ltd. All rights reserved.

'Keywords': Lithium and compounds; metalation; elimination reactions; rearrangements

The generation of α -alkoxy-substituted arylmethyl carbanions is the subject of controversial reports in the chemical literature. Indeed, Yeh reported some experiments showing α -lithiation of benzyl methyl ether with *n*-BuLi in hexane/TMEDA followed by trapping of the intermediate carbanion with electrophiles [1], but other authors pointed out the relative instability of similar organometallics, especially when generated in THF. Under these conditions, 1.2-Wittig rearrangement or β -elimination of such carbanions are expected to produce alkoxides. Schöllkopf [2,3] and Landsbury [4] independently investigated the rearrangement of α -metallated alkyl benzyl ethers and established that migratory aptitudes of alkyl residues increase with the relative stability of the resulting radicals (e.g., methyl <ethyl < isopropyl < tert-butyl). Furthermore, they investigated the competing decay of metalated primary and secondary alkyl benzyl ethers to alkenes and benzyl alcohol, and found that α -metalated benzyl *n*-alkyl ethers are more prone to β -eliminaton then α metalated benzyl sec-alkyl ethers [3,4]. Following these findings, other groups developed elaborate procedures to generate synthetic analogues of these carbanions [5-7]. Further improvent of one of these procedures (*i.e.*, metalation of (benzyl methyl ether)tricarbonylchromium(0) [5]) led to the development of asymmetric functionalization of the benzylic methylene group [8].

On the other hand, we have reported that stable α -methoxy-arylmethyllithium derivatives can be generated in THF at -40 °C either by the reductive cleavage of aromatic dimethyl acetals [9], or by the metalation of methyl arylmethyl ethers with alkyllithium bases [10]. More recently, Krief reported the successful generation of α -methoxy- α -phenylalkyllithium derivatives by C-Se bond exchange with *t*-BuLi in THF at -78 °C [11,12].

Given that the deaggregation of organometallics by a coordinated solvent like THF is of prime importance for their reactivity [13,14], we wish now to report full experimental details concerning the metalation of several arylmethyl alkyl ethers in THF and to show that, besides the choice of suitable alkyl substituents, a careful control of reaction time and temperature is critical to avoid side reactions.

Results and Discussion

Arylmethyl alkyl ethers were synthesized according to known procedures: ethers 1a-1c and 1j were obtained by reaction of arylmethyl chlorides with sodium alkoxide in the corresponding alcohol [15]; methyl ethers 1d-1i were synthesized by the reaction of sodium arylmethoxides with CH₃I [16]; the chloroether 1l was obtained by reaction of benzyl 3-hydroxypropyl ether with thionyl chloride [17]. Metalations were carried out under Ar in the presence of an excess (1.2 - 2.8 equiv) of *n*-BuLi or *sec*-BuLi in dry THF.



Scheme 1: 1a, 2a, $R = CH_3$; 1b, 2b, $R = C_2H_5$; 1c, 2c, $R = CH(CH_3)_2$ β -Elimination is possible only for compounds 1b and 1c

Metalation of Benzyl Alkyl Ethers la-c.

We first investigated the behaviour under different metalation conditions of benzyl methyl ether **1a**, of benzyl ethyl ether **1b** (a primary alkyl benzyl ether) and of isopropyl benzyl

ether 1c (a secondary alkyl benzyl ether) to gain insights into the influence of the alkyl chain on the metalation reaction. The results are reported in Table 1 (Scheme 1).

Methyl ether 1a, was metalated with 1.2 to 2 equiv of alkyllithium in dry THF and the resulting mixtures were quenched with H₂O or D₂O. Crude products were subjected to ¹H-NMR spectroscopic analyses to determine the relative amounts of starting material and of Wittig rearrangement product (1-phenylethanol 2a). Our results show that compound 2a is the main product of a room temperature reaction whilst, at -20 °C, its relative amount decreases to 24% (Table 1, entries 1 and 2). The intermediate formation of α -methoxy- α -phenyllithium is almost quantitative at -40 °C within 1 h reaction time (Table 1, entries 3 and 4). More prolonged reaction times led to slow protonation of the above mentioned organometallic derivative, as well as to the formation of significant amounts of 2a (Table 1, entries 5 and 6).

Metalation of benzyl ethyl ether 1b, afforded different results. Indeed, reaction of 1b with 1.2 equiv of *n*-BuLi at -40 °C for 1 h in THF gave both the rearranged product (1-phenyl-1-propanol 2b) and the product of β -elimination (benzyl alcohol 3) in *ca.* 1 : 4.4 ratio (Table 1, entry 7). Lowering the temperature to -80 °C completely suppressed the rearrangement of the intermediate carbanion, but not the β -elimination reaction path, as demonstrated by the recovery of significant amounts of alcohol 3 (Table 1, entry 8).

Entry	Compd	Equiv of	T (°C)	t (h)	Product Distribution (%) ^a		
		n-BuLi			1 (%D) ^b	2	3
1	1a	2	25	1	-	71 ^c	-
2	1a	2	-20	1	76 (>95)	24	-
3	1a	2	-40	1	>95 (>95)	<5	-
4	1a	1.2	-40	1	>95 (>95)	<5	-
5	1a	2	-40	6	92 (92)	8	-
6	1a	2	-40	24	78 (73)	22	-
7	16	1.2	-40	1	30 (n.d.)	13	57
8	1 b	1.2	-80	3	46 (28)	-	26
9	1 c	1.4d	-40	1	-	28	72
10	1 c	1.4d	-80	3	>95 (>95)	-	<5

 Table 1.

 Products Distribution in the Metalation Reaction of Compound 1a-1c

^aProduct distribution was determined by ¹H NMR spectroscopic analyses of crude reaction mixtures, unless otherwise indicated.

^bAs determined by ¹H NMR spectroscopy by monitoring the percentage of deuterium incorporation in the benzylic position after D₂O quenching; n.d. means not determined.

^cIsolated yield.

^dSec-BuLi was employed instead of *n*-BuLi.

Metalation of isopropyl benzyl ether 1d, with *sec*-BuLi in THF at -40 °C for 1 h afforded both the Wittig rearrangement product (1-phenyl-2-methylpropanol 2c) and alcohol 3 in *ca*. 1 : 2.5 ratio (Table 1, entry 9). Lowering the temperature to -80 °C completely suppressed the rearrangement of the intermediate organometallic species and reduced formation of alcohol 3 to a minimal amount. Under these reaction conditions, formation of α -metallated isopropyl benzyl ether is quantitative (Table 1, entry 10).

Our results show that reaction temperature is a crucial parameter in the generation of stable α -metalated alkyl benzyl ethers. Working at low temperature is generally useful to avoid their 1,2-rearrangement, as well as β -elimination of secondary alkyl benzyl ethers, but ineffective in avoiding β -elimination of α -metalated *n*-alkyl benzyl ethers. The last finding is in agreement with the observations on the relative propensity towards β -elimination of α -metallated benzyl alkyl ethers reported by Schöllkopf and Landsbury (see above) [2,4].

Metalation/Electrophilic Substitution of Arylmethyl Alkyl Ethers.

To improve the usefulness of the above results, we investigated the alkyllithium promoted electrophilic substitution of several arylmethyl alkyl ethers. We performed the metalations as described above, and quenched the reaction mixtures with D_2O (2 mL) or with 1.1 equiv of other electrophiles, before work up and purification. The results are reported in Table 2 (Scheme 2). We were able to trap the organometallic generated by the action of *n*-BuLi or *sec*-BuLi on 1a at -40 °C with CH₃I (Table 2, entry 1), with primary and secondary alkyl halides (Table 2, entries 2 and 3), with ethylene oxide (Table 2, entry 4), with enolizable and non-enolizable carbonyl derivatives (Table 2, entries 5 and 6). Similarly, quenching with *n*-BuBr the reaction mixture obtained by the metalation of 1c at -80 °C afforded the desired product in satisfactory yield (Table 2, entry 7).

We have also investigated the behaviour, under similar conditions, of alkyl- (1d, 1e), alkoxy- (1f-1h) and halo- (1i, 1j) substituted arylmethyl methyl ethers. In all cases, we found conditions leading to the formation of stable α -metalated arylmethyl methyl ethers in quantitative to satisfactory yields, as evidenced by the results of the metalation/substitution reactions reported (Table 2, entries 8-23). All methyl ethers were metallated at -40 °C, with the exception of compounds 1h-1j (Table 2, entries 17-23), requiring a lower reaction temperature to afford the desired products in satisfactory yields.



Scheme 2. Reagents: i, AlkylLi excess, THF; ii, EX, then H2O

Entry	Compd	$\mathbf{R}^1 = a$	AlkylLi (equiv)	T (°C)	t (h)	EXb	Product, E =	Yield (%) ^c
1	1 a	н	sec-BuLi (1.2)	-40	1	CH3I	4aa, CH3	87
2	1a	н	n-BuLi (1.2)	-40	1	C4H9Br	4ab , C4H9	68
3	1a	н	<i>sec</i> -BuLi (1.2)	-40	1	(CH3)2CHBr	4ac, (CH3)2CH	61
4	1a	н	n-BuLi (1.2)	-40	1	ethylene oxided	4ad, CH ₂ CH ₂ OH	45
5	1a	Н	n-BuLi (1.2)	-40	1	(CH3)2CO	4ae, (CH3)2COH	53
6	1a	н	n-BuLi (1.2)	-40	1	(C6H5)2CO	4af , (C6H5)2COH	76
7	1 c	H ^e	sec-BuLi (1.4)	-80	3	C4H9Br	4ca, C4H9	79
8	1 d	4-CH3	n-BuLi (1.2)	-40	I	D20	4da , D	90 ^f
9	1d	4-CH3	sec-BuLi (1.2)	-40	1	CH ₃ I	4db, CH3	>95
10	1d	4-CH3	n-BuLi (1.2)	-40	1	C4H9Br	4dc, C4H9	80
11	1 e	2-CH3	n-BuLi (1.2)	-40	1	D20	4ea , D	88 ^f
12	1 e	2-CH3	sec-BuLi (1.2)	-40	1	CH3I	4eb , CH ₃	86
13	1 f	4-CH3O	sec-BuLi (1.4)	-40	5	D20	4fa , D	80f
14	1f	4-CH3O	sec-BuLi (1.4)	-40	5	C4H9Brg	4fb, C4H9	77
15	1 g	2-CH3O	n-BuLi (1.2)	-40	1	D ₂ O	4ga , D	85 <i>f</i>
16	1 g	2-CH3O	n-BuLi (1.2)	-40	1	C4H9Br	4gb, C4H9	80
17	1 h	3,5-(CH3O)2	sec-BuLi (1.2)	-80	4	D ₂ O	4ha , D	91 <i>f</i>
18	1 h	3,5-(CH3O)2	sec-BuLi (1.3)	-80	4	C4H9Br	4hb , C4H9	72
19	1 i	4-Cl	sec-BuLi (1.2)	-80	4	D ₂ O	4ia , D	>95 ^f
20	1 i	4-Cl	sec-BuLi (1.2)	-80	4	t-BuCHO	4ib, t-BuCHOH	87 ^h
21	1 i	4-Cl	sec-BuLi (1.2)	-80	4	PhCHO	4ic, PhCHOH	68 ⁱ
22	1j	4-F	sec-BuLi (2.8)	-80	7	(CH3)3SiCl	4ja , (CH3)3Si	68 ¹
23	1 j	4-F	sec-BuLi (2.8)	-80	7	CI(CH ₂) ₄ Cl	4jb, Cl(CH ₂)4	35

 Table 2

 Metalatation/Electrophilic Substitution of Arylmethyl Alkyl Ethers 1a, 1c-i

 $a_{R} = CH_{3}$, unless otherwise indicated.

 $b_{\text{Reaction time}} = 10 \text{ min.}$

^cIsolated yields, unless otherwise noted.

dGaseous ethylene oxide was bubbled into the reaction mixture for 5 min.

 $e_{\rm R} = ({\rm CH}_3)_2 {\rm CH}.$

 f_{As} determined by ¹H NMR spectroscopy by monitoring the percentage of deuterium incorporation in the benzylic position after D₂O quenching.

8 The electrophile was added at -80 °C.

hA diastereoisomeric mixture (65:35 by ¹H NMR spectroscopy) was obtained.

 i A diastereo-isomeric mixture (58:42 by 1 H NMR spectroscopy) was obtained.

¹As determined by ¹H NMR spectroscopic analysis of the crude reaction mixtures.

The regioselectivity observed in the metalation of substituted arylmethyl methyl ethers reported above deserves some comments. Careful inspection of ¹H NMR spectra of crude reaction mixtures shows that toluene derivatives **1d** and **1e** were regioselectively metalated at the ethereal benzylic position, with no evidences of substitution at the methyl group.

Similarly, otherwise substituted arylmethyl methyl ethers were regioselectively metalated too, with no evidence of substitution at the aromatic ring, and we conclude that ring proton abstraction is not a serious drawback of these reactions. These are interesting findings, in view of the known competition between lateral and ring proton abstraction observed in the metalation of substituted toluenes [13,18], and show that the ether moiety is a very effective metalation director in arylmethyl substitution chemistry [19]. From this point of view, it is of interest to recall that, according to commonly accepted definitions, alkoxy-, fluorine- and chlorine-substituents are considered *ortho*-directing metalation groups of moderate strenghth [20], and that regioselective metalation of the methyl group of, *e.g.*, fluoro- or methoxy-substituted toluenes cannot be achieved with simple alkyllithium reagents, but requires the employment of the more complex butyllithium/diisopropylamine/potassium *tert*-butoxide base (LIDAKOR) [18,19, 21,22].

Finally, we have investigated the metalation reaction of 3-chloropropyl benzyl ether 11, as an attempt to trap, by means of intramolecular alkylation, a primary α -alkoxy- α benzyllithium (Scheme 3). However, metalation of 11 under various reaction conditions (THF, -80°C, 2h; hexane, -40 °C, 4h) afforded an intermediate carbanion which undergoes a very rapid β -elimination to benzyl alcohol 3, so that we were unable to observe the formation of the desired 2-phenyltetrahydrofuran, 5 [23].



Scheme 3. Attempted metalation/intramolecular electrophilic substitution of compound 11

It is therefore evident that, under the reported set of reaction conditions, β -elimination is an unavoidable reaction path of primary α -alkoxy- α -arylmethyllithium derivatives.

EXPERIMENTAL PART

General.

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillations are given as boiling points. Starting materials were of the highest commercial quality and were used without further purification. D₂O was 99.8% isotopic purity. THF

was distilled from Na/K alloy under N₂ immediately prior to use. Ethers were prepared according to general procedures described in references 15 (**1a-c**, **1j**), 16 (**1d-1i**) and 17 (**11**). ¹H NMR spectra were recorded at 300 MHz and ¹³C NMR spectra were recorded at 75 MHz in CDCl₃ with SiMe₄ as internal standard. Deuterium incorporation was calculated by monitoring the ¹H NMR spectra of the crude mixtures and comparing the integration of the signal corresponding to the protons in the arylmethyl position with that of known signals. Resonances of the CHD protons are usually shifted 0.02-0.04 ppm (δ) upfield relative to the resonances of the corresponding arylmethyl CH₂ protons. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Metalation of Ethers 1 and Reaction with Electrophiles. General Procedure.

The substrate (10 mmol) was dissolved under Ar in dry THF (20 - 30 mL) and chilled to the temperature reported in Table 1 or 2. To this mixture 1.2 - 2.8 equiv of a solution of the appropriate alkyllithium reagent (*n*-BuLi 1.6 M in hexane; *sec*-BuLi 1.3 M in cyclohexane) was added. After stirring for the reported time, the appropriate electrophile (1.1 equiv), dissolved in dry THF (5 mL), was added dropwise. After stirring for 10 minutes, the mixture was quenched by slow dropwise addition of H₂O (10 mL, *caution!*), the cold bath removed, and the resulting mixture extracted with Et₂O (3 x 30 mL). The organic phase was dried (Na₂SO₄) and the solvent evaporated. Crude products were purified by distillation or flash chromatography (silica gel, hexane/AcOEt). Compounds **4aa** [24], **4ab** [1] and **4af** [1], have already been described. Other products were purified and characterized as follows.

1-Phenyl-2-methylpropyl Methyl Ether (4ac). Purified by flash chromatography (hexane/AcOEt = 9:1); bp 95 °C/10 mmHg; $\delta_{\rm H}$ 0.65 (3 H, d, J = 6.8 Hz, CH₃C), 0.91 (3 H, d, J = 6.8 Hz, CH₃C), 1.84 (1 H, oct, J = 6.8 Hz, CH), 3.11 (3 H, s, CH₃O), 3.67 (1 H, d, J = 6.8 Hz, CHO), 7.14-7.28 (5 H, m, ArH); $\delta_{\rm C}$ 18.9, 18.9, 34.7, 56.9, 89.7, 127.3, 127.4, 128.0, 141.0; Anal. Calcd. for C₁₁H₁₆O: C, 80.42; H, 9.84. Found: C, 80.67; H, 10.03.

1-Phenyl-3-hydroxypropyl Methyl Ether (4ad). Purified by flash chromatography (hexane/AcOEt = 7:3); bp 160 °C/10 mmHg; v (CCl₄) 3632 and 3528 (OH) cm⁻¹; $\delta_{\rm H}$ 1.80-1.92 (1 H, m, *CH*-H), 1.98-2.12 (1 H, m, *CH*-H), 2.62, (1 H, br s, OH), 3.24 (3 H, s, CH₃), 3.78 (2 H, t, J = 5.4 Hz, CH₂O), 4.39 (1 H, dd, J = 4.5, 4.2 Hz, CH), 7.28-7.38 (5 H, m, ArH); $\delta_{\rm C}$ 40.4, 56.6, 61.2, 83.9, 126.5, 127.7, 128.5, 141.4; identical in all respects to an authentic sample synthesized according to a general procedure described in ref. 6.

1-Phenyl-2-methyl-2-hydroxypropyl Methyl Ether (4ae). Purified by fractional distillation; bp 195 °C/10 mmHg; v (neat) 3456 (OH) cm⁻¹; $\delta_{\rm H}$ 1.00 (3 H, s, CH₃C), 1.07 (3 H, s, CH₃C), 2.38 (1 H, br s, OH), 3.19 (3 H, s, CH₃O), 3.91 (1 H, s, CH), 7.18-7.29 (5 H, m, ArH); $\delta_{\rm C}$ 24.0, 26.0, 57.4, 72.8, 90.7, 127.8, 127.9, 128.1, 137.9; Anal. Calcd. for C₁₁H₁₆O₂: C, 73.28; H, 8.96. Found: C, 73.12; H, 9.07.

1-Phenylpentyl Isopropyl Ether (4ca). Purified by flash chromatography (hexane/AcOEt = 9.5:0.5); bp 75 °C/1 mmHg; $\delta_{\rm H}$ 0.87 (3 H, t, J = 6.9 Hz, CH_3CH_2), 1.07 (3 H, d, J = 6.3 Hz, CH_3CH), 1.14 (3 H, d, J = 6.3 Hz, CH_3CH), 1.19-1.41 (4 H, m, (CH₂)₂), 1.52-1.80 (2 H, m, CH₂), 3.45 (1 H, sept, J = 6.3 Hz, $CH(CH_3)_2$), 4.29 (1 H, dd, J = 9 Hz, 5.4 Hz, CH), 7.22-7.36 (5 H, m, ArH); $\delta_{\rm C}$ 14.0, 21.2, 22.6, 23.5, 28.2, 38.6, 68.7, 79.3, 126.6, 127.1, 128.2, 144.1; Anal. Calcd. for C₁₄H₂₂O: C, 81.48; H, 10.77. Found: C, 81.76; H, 10.45.

1-(4-Methylphenyl)ethyl Methyl Ether (4db). Purified by flash chromatography (hexane/AcOEt = 9.5:0.5); bp 80 °C/10 mmHg; $\delta_{\rm H}$ 1.42 (3 H, d, J = 6.6 Hz, CH₃), 2.35 (3 H, s, CH₃Ar), 3.21 (3 H, s, CH₃O), 4.26 (1 H, q, J = 6.6 Hz, CH), 7.15-7.22 (4 H, m, ArH); identical in all respects to an authentic sample synthesized according to a general procedure described in ref. 6.

1-(4-Methylphenyl)pentyl Methyl Ether (4dc). Purified by flash chromatography (hexane/AcOEt = 9.5:0.5); bp 125 °C/10 mmHg; $\delta_{\rm H}$ 0.86 (3 H, t, J = 7.2 Hz, CH₃), 1.18-1.40 (4 H, m, (CH₂)₂), 1.55-1.68 (1 H, m, CHCHO), 1.72-1.77 (1 H, m, CHCHO), 2.35 (3 H, s, CH₃Ar), 3.18 (3 H, s, CH₃O), 4.26 (1 H, m, CHO), 7.16 (4 H, br s, ArH); $\delta_{\rm C}$ 14.0, 21.1, 22.6, 28.0, 37.9, 56.5, 84.0, 126.7, 129.0, 137.0, 139.4; identical in all respects to an authentic sample synthesized according to a general procedure described in ref. 6.

1-(2-Methylphenyl)ethyl Methyl Ether (4eb). Purified by distillation, bp 80 °C/10 mmHg; $\delta_{\rm H}$ 1.40 (3 H, d, J = 6.6 Hz, CH₃), 2.33 (3 H, s, CH₃Ar), 3.23 (3 H, s, CH₃O), 4.56 (1 H, q, J = 6.6 Hz, CH), 7.12-7.25 (3 H, m, ArH), 7.37-7.41 (1 H, m, ArH); identical in all respects to an authentic sample synthesized according to a general procedure described in ref. 6.

1-(4-Methoxyphenyl)pentyl Methyl Ether (4fb). Purified by flash chromatography (hexane/AcOEt = 9:1); bp 95 °C/1 mmHg; $\delta_{\text{H}:}$ 0.86 (3 H, t, J = 7.2 Hz, CH_3CH_2), 1.12-1.40 (4 H, m, (CH₂)₂), 1.52-1.66 (1 H, m, CH), 1.74-1.87 (1 H, m, CH), 3.17 (3 H, s, CH_3OCH), 3.81 (3 H, s, CH₃OAr), 4.02 (1 H, t, J = 6.9 Hz, CHO), 6.86-6.91 (2 H, m, ArH), 7.17-7.22 (2 H, m, ArH); $\delta_{\text{C}:}$ 14.0, 22.6, 28.0, 37.8, 55.1, 56.3, 83.6, 113.6, 127.8, 134.4, 158.9. Anal. Calcd. for C₁₃H₂₀O₂: C, 74.94; H, 9.70. Found: C = 75.06; H, 9.78.

1-(2-Methoxyphenyl)pentyl Methyl Ether (4gb). Purified by flash chromatography (hexane/AcOEt = 7:3); bp 100 °C/1 mmHg; $\delta_{\text{H}:}$ 0.87 (3 H, t, J = 6.6 Hz, CH_3 CH₂), 1.28-1.35 (4 H, m, (CH₂)₂), 1.64-1.67 (2 H, m, CH), 3.23 (3 H, s, CH_3 OCH), 3.82 (3 H, s, CH₃OAr), 4.60 (1 H, t, J = 6.0 Hz, CHO), 6.86 (1 H, dd, J = 8.4, 1.0 Hz, ArH), 6.98 (1 H, td, J = 8.4, 1.5 Hz, ArH), 7.23 (1 H, td, J = 8.0, 1.5 Hz, ArH), 7.32 (1 H, dd, J = 6.4, 1.5 Hz, ArH); $\delta_{\text{C}:}$ 14.0, 22.6, 27.9, 36.7, 55.2, 56.7, 77.2, 110.2, 120.6, 126.4, 127.8, 130.8, 157.0. Anal. Calcd. for C₁₃H₂₀O₂: C, 74.94; H, 9.70. Found: C = 75.10; H, 9.63; identical in all respects to an authentic sample synthesized according to a general procedure described in ref. 6.

1-(3,5-Dimethoxyphenyl)pentyl Methyl Ether (4hb). Purified by flash chromatography (hexane/AcOEt = 8:2); bp 145 °C/1 mmHg; $\delta_{\text{H}:}$ 0.87 (3 H, t, J = 7.0 Hz

CH3), 1.18-1.42 (4 H, m, (CH₂)₂), 1.54-1.68 (1 H, m, CH), 1.72-1.84 (1 H, m, CH), 3.22 (3 H, s, *CH*₃OCH), 3.80 (6 H, s, 2 x CH₃OAr), 4.00 (1 H, dd, J = 5.7, 7.2 Hz, ArCH), 6.37 (1 H, t, J = 2.4 Hz, ArH), 6.45 (2 H, d, J = 2.4 Hz ArH); δ_{C} : 14.0, 22.6, 28.0, 37.8, 55.3, 56.7, 84.2, 99.2, 104.5, 145.3, 160.8. Anal. Calcd. for C₁₄H₂₂O₃: C, 70.54; H, 9.32. Found: C = 70.61; H, 9.28.

1-(4-Chlorophenyl)-2-hydroxy-3,3-dimethylbutyl Methyl Ether (4ib). Purified by flash chromatography (hexane/AcOEt = 9:1); first diastereoisomer eluted: bp 160 °C/1 mmHg; v (film) 3494 (OH) cm⁻¹; $\delta_{\rm H}$ 0.91 (9 H, s, C(CH₃)₃), 3.22 (3 H, s, CH₃O), 3.23 (1 H, d, J = 3.6 Hz, CHOH), 4.17 (1 H, d, J = 3.6 Hz, CHAr), 7.25-7.29 (2 H, m, ArH), 7.31-7.35 (2 H, m, ArH). $\delta_{\rm C}$ 26.5, 35.0, 56.2, 81.7, 82.2, 128.5, 128.7, 133.7, 139.6. Second diastereoisomer eluted: bp 160 °C/1mmHg; v (film) 3494 (OH) cm⁻¹; $\delta_{\rm H}$ 0.91 (9 H, s, C(CH₃)₃), 3.13 (3 H, s, OCH₃), 3.51 (1 H, d, J = 6.0 Hz, CHOH), 4.10 (1 H, d, J = 6.0 Hz, CHAr), 7.25-7.29 (2 H, m, ArH), 7.31-7.35 (2 H, m, ArH); $\delta_{\rm C}$ 26.6, 34.6, 56.1, 80.8, 84.4, 128.6, 130.01 134.0, 138.2. Anal. Calcd. for C_{13H19}ClO₂: C, 64.31; H, 7.90. Found: C = 64.27; H, 7.98.

1-(4-Chlorophenyl)-2-hydroxy-2-phenylethyl Methyl Ether (4ic). Purified by flash chromatography (hexane/AcOEt = 8:2); first diastereoisomer eluted: bp 185 °C/1 mmHg; v (film) 3408 (OH) cm⁻¹; $\delta_{\rm H}$ 3.24 (3 H, s, CH₃O), 4.32 (1 H, d, J = 4.8 Hz, CH), 4.91 (1 H, d, J = 4.8 Hz, CH), 6.99-7.05 (2 H, m, ArH), 7.10-7.15 (2 H, m, ArH), 7.20-7.28 (5 H, m, ArH); $\delta_{\rm C}$ 57.2, 76.7, 87.0, 126.9, 127.7, 127.9, 128.1, 129.3, 133.7, 135.7, 139.9. Second diastereoisomer eluted: bp 185 °C/1mmHg; v (film) 3410 (OH) cm⁻¹; $\delta_{\rm H}$ 3.29 (3 H, s, CH₃O), 4.10 (1 H, d, J = 8.2 Hz, CH), 4.59 (1 H, d, J = 8.2 Hz, ArCH), 6.88-6.95 (2 H, m, ArH), 7.00-7.06 (2 H, m, ArH), 7.15-7.20 (5 H, m, ArH); $\delta_{\rm C}$ 57.0, 78.6, 88.6, 127.3, 127.9, 128.0, 128.3, 129.0, 133.8, 136.1, 138.9. Anal. Calcd. for C₁₅H₁₅ClO₂: C, 68.56; H, 5.77. Found: C = 68.39; H, 5.82.

(4-Fluorophenyl)trimethylsilylmethyl Methyl Ether (4ja). Purified by flash chromatography (hexane/CH₂Cl₂ = 6:4); bp 160 °C/760 mmHg; $\delta_{\rm H}$ -0.05 (9 H, s, Si(CH₃)₃), 3.26 (3 H, s, CH₃O), 3.89 (1 H, s, CH), 6.94-7.03 (2 H, m, ArH), 7.04-7.13 (2 H, m, ArH); $\delta_{\rm C}$ 59.1, 80.1, 115,1 (d, J = 21 Hz), 127.1 (d, J = 8 Hz), 136.9 (d, J = 3 Hz), 162.8 (d, J = 243 Hz). Anal. Calcd. for C₁₁H₁₇FOSi: C, 62.21; H, 8.08. Found: C = 61.96; H, 8.11.

1-(4-Fluorophenyl)-4-chloropentyl Methyl Ether (4jb). Purified by flash chromatography (hexane/AcOEt = 8:2); bp 145 °C/1 mmHg; v (film) 1220 (ArF) cm⁻¹; $\delta_{\rm H}$ 1.30-1.87 (6 H, m, (CH₂)₃), 3.19 (3 H, s, CH₃), 3.50 (2 H, t, J = 6.6 Hz, CH₂Cl), 4.07 (1 H, dd, J = 7.5, 5.4 Hz, CH), 6.99-7.08 (2 H, m, ArH), 7.21-7.28 (2 H, m, ArH); $\delta_{\rm C}$ 23.2, 32.5, 37.4, 44.9, 56.6, 83.1, 115.2 (d, J = 22 Hz), 128.2 (d, J = 8 Hz), 137.8 (d, J = 3 Hz), 162.2 (d, J = 244 Hz). Anal. Calcd. for C₁₂H₁₆ClFO: C, 62.46; H, 7.00. Found: C = 62.25; H, 7.08.

Aknowledgments: We are indebted to the Ministero dell'Università e Ricerca Scientifica (MURST, 60% funds) and to the Regione Autonoma della Sardegna (L.R. n. 43) for financial support. L. P. and A. S. are the recipients of a fellowship from R.A.S.

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