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Metalation of Arylmethyl Alkyl Ethers

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Abstract. Arylmethyl alkyl ethers **1a-1l** 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**.

'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)tricarbonyl-chromium(0) [5]) led to the development of asymmetric functionalization of the benzylic methylene group [8].

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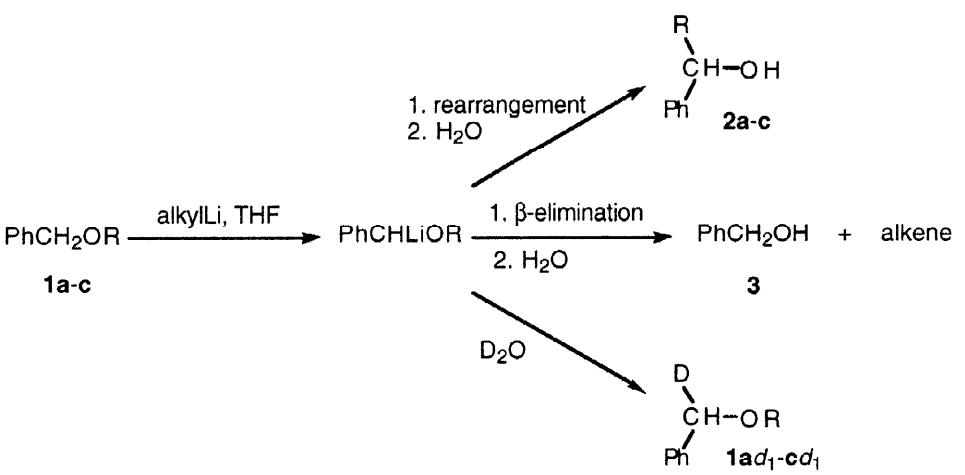
On the other hand, we have reported that stable α-methoxy-arylmethyllithium derivatives can be generated in THF at -40 °C either by the reductive cleavage of aromatic dimethyl acetals [9], or by the metalation of methyl arylmethyl ethers with alkyllithium bases [10]. More recently, Krief reported the 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 CH_3I [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 ***1a-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 H_2O or D_2O. 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).

Table 1.

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

Entry	Compd	Equiv of *n*-BuLi	T (°C)	t (h)	Product Distribution (%)[a]		
					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	**1b**	1.2	-40	1	30 (n.d.)	13	57
8	**1b**	1.2	-80	3	46 (28)	-	26
9	**1c**	1.4[d]	-40	1	-	28	72
10	**1c**	1.4[d]	-80	3	>95 (>95)	-	<5

[a]Product distribution was determined by ^1H NMR spectroscopic analyses of crude reaction mixtures, unless otherwise indicated.

[b]As determined by ^1H NMR spectroscopy by monitoring the percentage of deuterium incorporation in the benzylic position after D_2O quenching; n.d. means not determined.

[c]Isolated yield.

[d]*Sec*-BuLi was employed instead of *n*-BuLi.

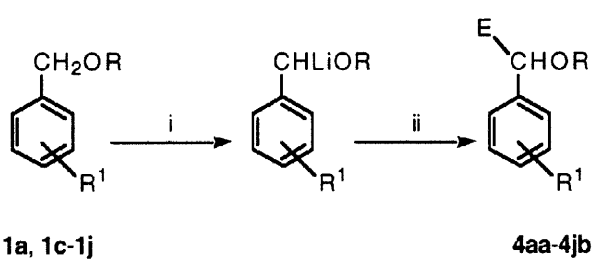
Metalation of isopropyl benzyl ether **1d**, with *sec*-BuLi in THF at -40 °C for 1 h afforded both the Wittig rearrangement product (1-phenyl-2-methylpropanol **2c**) and alcohol **3** in *ca.* 1 : 2.5 ratio (Table 1, entry 9). Lowering the temperature to -80 °C completely suppressed the rearrangement 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 CH_3I (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.



1a, 1c-1j **4aa-4jb**

Scheme 2. *Reagents*: i, AlkylLi excess, THF; ii, EX, then H_2O

Table 2

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

Entry	Compd	R^1 = [a]	AlkylLi (equiv)	T (°C)	t (h)	EX[b]	Product, E =	Yield (%)[c]
1	**1a**	H	*sec*-BuLi (1.2)	-40	1	CH_3I	**4aa**, CH_3	87
2	**1a**	H	*n*-BuLi (1.2)	-40	1	C_4H_9Br	**4ab**, C_4H_9	68
3	**1a**	H	*sec*-BuLi (1.2)	-40	1	$(CH_3)_2CHBr$	**4ac**, $(CH_3)_2CH$	61
4	**1a**	H	*n*-BuLi (1.2)	-40	1	ethylene oxide[d]	**4ad**, CH_2CH_2OH	45
5	**1a**	H	*n*-BuLi (1.2)	-40	1	$(CH_3)_2CO$	**4ae**, $(CH_3)_2COH$	53
6	**1a**	H	*n*-BuLi (1.2)	-40	1	$(C_6H_5)_2CO$	**4af**, $(C_6H_5)_2COH$	76
7	**1c**	H[e]	*sec*-BuLi (1.4)	-80	3	C_4H_9Br	**4ca**, C_4H_9	79
8	**1d**	4-CH_3	*n*-BuLi (1.2)	-40	1	D_2O	**4da**, D	90[f]
9	**1d**	4-CH_3	*sec*-BuLi (1.2)	-40	1	CH_3I	**4db**, CH_3	>95
10	**1d**	4-CH_3	*n*-BuLi (1.2)	-40	1	C_4H_9Br	**4dc**, C_4H_9	80
11	**1e**	2-CH_3	*n*-BuLi (1.2)	-40	1	D_2O	**4ea**, D	88[f]
12	**1e**	2-CH_3	*sec*-BuLi (1.2)	-40	1	CH_3I	**4eb**, CH_3	86
13	**1f**	4-CH_3O	*sec*-BuLi (1.4)	-40	5	D_2O	**4fa**, D	80[f]
14	**1f**	4-CH_3O	*sec*-BuLi (1.4)	-40	5	C_4H_9Br[g]	**4fb**, C_4H_9	77
15	**1g**	2-CH_3O	*n*-BuLi (1.2)	-40	1	D_2O	**4ga**, D	85[f]
16	**1g**	2-CH_3O	*n*-BuLi (1.2)	-40	1	C_4H_9Br	**4gb**, C_4H_9	80
17	**1h**	3,5-$(CH_3O)_2$	*sec*-BuLi (1.2)	-80	4	D_2O	**4ha**, D	91[f]
18	**1h**	3,5-$(CH_3O)_2$	*sec*-BuLi (1.3)	-80	4	C_4H_9Br	**4hb**, C_4H_9	72
19	**1i**	4-Cl	*sec*-BuLi (1.2)	-80	4	D_2O	**4ia**, D	>95[f]
20	**1i**	4-Cl	*sec*-BuLi (1.2)	-80	4	*t*-BuCHO	**4ib**, *t*-BuCHOH	87[h]
21	**1i**	4-Cl	*sec*-BuLi (1.2)	-80	4	PhCHO	**4ic**, PhCHOH	68[i]
22	**1j**	4-F	*sec*-BuLi (2.8)	-80	7	$(CH_3)_3SiCl$	**4ja**, $(CH_3)_3Si$	68[l]
23	**1j**	4-F	*sec*-BuLi (2.8)	-80	7	$Cl(CH_2)_4Cl$	**4jb**, $Cl(CH_2)_4$	35

[a] R = CH_3, unless otherwise indicated.

[b] Reaction time = 10 min.

[c] Isolated yields, unless otherwise noted.

[d] Gaseous ethylene oxide was bubbled into the reaction mixture for 5 min.

[e] R = $(CH_3)_2CH$.

[f] As determined by ^1H NMR spectroscopy by monitoring the percentage of deuterium incorporation in the benzylic position after D_2O quenching.

[g] The electrophile was added at -80 °C.

[h] A diastereoisomeric mixture (65:35 by ^1H NMR spectroscopy) was obtained.

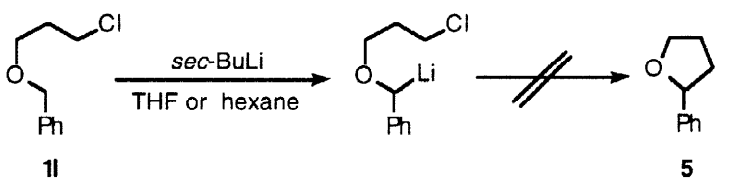
[i] A diastereo-isomeric mixture (58:42 by ^1H NMR spectroscopy) was obtained.

[l] As 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 **1l**, as an attempt to trap, by means of intramolecular alkylation, a primary α-alkoxy-α-benzyllithium (Scheme 3). However, metalation of **1l** 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].



1l **5**

Scheme 3. Attempted metalation/intramolecular electrophilic substitution of compound **1l**

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. D_2O was 99.8% isotopic purity. THF

was distilled from Na/K alloy under N_2 immediately prior to use. Ethers were prepared according to general procedures described in references 15 (**1a-c, 1j**), 16 (**1d-1i**) and 17 (**1l**). ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $SiMe_4$ 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 CH_2 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 H_2O (10 mL, *caution!*), the cold bath removed, and the resulting mixture extracted with Et_2O (3 x 30 mL). The organic phase was dried (Na_2SO_4) 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; δ_H 0.65 (3 H, d, *J* = 6.8 Hz, CH_3C), 0.91 (3 H, d, *J* = 6.8 Hz, CH_3C), 1.84 (1 H, oct, *J* = 6.8 Hz, CH), 3.11 (3 H, s, CH_3O), 3.67 (1 H, d, *J* = 6.8 Hz, CHO), 7.14-7.28 (5 H, m, ArH); δ_C 18.9, 18.9, 34.7, 56.9, 89.7, 127.3, 127.4, 128.0, 141.0; Anal. Calcd. for $C_{11}H_{16}O$: 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; ν (CCl_4) 3632 and 3528 (OH) cm^{-1}; δ_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, CH_3), 3.78 (2 H, t, *J* = 5.4 Hz, CH_2O), 4.39 (1 H, dd, *J* = 4.5, 4.2 Hz, CH), 7.28-7.38 (5 H, m, ArH); δ_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; ν (neat) 3456 (OH) cm^{-1}; δ_H 1.00 (3 H, s, CH_3C), 1.07 (3 H, s, CH_3C), 2.38 (1 H, br s, OH), 3.19 (3 H, s, CH_3O), 3.91 (1 H, s, CH), 7.18-7.29 (5 H, m, ArH); δ_C 24.0, 26.0, 57.4, 72.8, 90.7, 127.8, 127.9, 128.1, 137.9; Anal. Calcd. for $C_{11}H_{16}O_2$: 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; δ_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, $(CH_2)_2$), 1.52-1.80 (2 H, m, CH_2), 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); δ_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 $C_{14}H_{22}O$: 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; δ_H 1.42 (3 H, d, J = 6.6 Hz, CH_3), 2.35 (3 H, s, CH_3Ar), 3.21 (3 H, s, CH_3O), 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; δ_H 0.86 (3 H, t, J = 7.2 Hz, CH_3), 1.18-1.40 (4 H, m, $(CH_2)_2$), 1.55-1.68 (1 H, m, CHCHO), 1.72-1.77 (1 H, m, CHCHO), 2.35 (3 H, s, CH_3Ar), 3.18 (3 H, s, CH_3O), 4.26 (1 H, m, CHO), 7.16 (4 H, br s, ArH); δ_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; δ_H 1.40 (3 H, d, J = 6.6 Hz, CH_3), 2.33 (3 H, s, CH_3Ar), 3.23 (3 H, s, CH_3O), 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; δ_H: 0.86 (3 H, t, J = 7.2 Hz, CH_3CH_2), 1.12-1.40 (4 H, m, $(CH_2)_2$), 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, CH_3OAr), 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); δ_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 $C_{13}H_{20}O_2$: 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; δ_H: 0.87 (3 H, t, J = 6.6 Hz, CH_3CH_2), 1.28-1.35 (4 H, m, $(CH_2)_2$), 1.64-1.67 (2 H, m, CH), 3.23 (3 H, s, CH_3OCH), 3.82 (3 H, s, CH_3OAr), 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); δ_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 $C_{13}H_{20}O_2$: 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; δ_H: 0.87 (3 H, t, J = 7.0 Hz

CH_3), 1.18-1.42 (4 H, m, $(CH_2)_2$), 1.54-1.68 (1 H, m, CH), 1.72-1.84 (1 H, m, CH), 3.22 (3 H, s, *CH*$_3$OCH), 3.80 (6 H, s, 2 x CH_3OAr), 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 $C_{14}H_{22}O_3$: 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; ν (film) 3494 (OH) cm^{-1}; δ_H 0.91 (9 H, s, $C(CH_3)_3$), 3.22 (3 H, s, CH_3O), 3.23 (1 H, d, J = 3.6 Hz, *CH*OH), 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). δ_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; ν (film) 3494 (OH) cm^{-1}; δ_H 0.91 (9 H, s, $C(CH_3)_3$), 3.13 (3 H, s, OCH_3), 3.51 (1 H, d, J = 6.0 Hz, *CH*OH), 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); δ_C 26.6, 34.6, 56.1, 80.8, 84.4, 128.6, 130.01 134.0, 138.2. Anal. Calcd. for $C_{13}H_{19}ClO_2$: 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; ν (film) 3408 (OH) cm^{-1}; δ_H 3.24 (3 H, s, CH_3O), 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); δ_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; ν (film) 3410 (OH) cm^{-1}; δ_H 3.29 (3 H, s, CH_3O), 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); δ_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 $C_{15}H_{15}ClO_2$: C, 68.56; H, 5.77. Found: C = 68.39; H, 5.82.

(4-Fluorophenyl)trimethylsilylmethyl Methyl Ether (4ja). Purified by flash chromatography (hexane/CH_2Cl_2 = 6:4); bp 160 °C/760 mmHg; δ_H -0.05 (9 H, s, $Si(CH_3)_3$), 3.26 (3 H, s, CH_3O), 3.89 (1 H, s, CH), 6.94-7.03 (2 H, m, ArH), 7.04-7.13 (2 H, m, ArH); δ_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 $C_{11}H_{17}FOSi$: 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; ν (film) 1220 (ArF) cm^{-1}; δ_H 1.30-1.87 (6 H, m, $(CH_2)_3$), 3.19 (3 H, s, CH_3), 3.50 (2 H, t, J = 6.6 Hz, CH_2Cl), 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); δ_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 $C_{12}H_{16}ClFO$: C, 62.46; H, 7.00. Found: C = 62.25; H, 7.08.

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