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Ion pairing effects on the regioselectivity of arylic versus benzylic C–O bond reductive cleavage: synthetic applications

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Dedicated to Professor Domenico Spinelli on the occasion of his 75th birthday

Abstract—The regioselectivity of the reductive cleavage of 3,4,5-trimethoxybenzyl methyl ether strongly depends on the alkali metal employed as a reducing agent and solvent effects. Reactions run using Na as a reducing agent led to aromatic C(4)–O bond cleavage, whilst reductions run in the presence of Na/15-crown-5, or using Li as a reducing agent, led to highly regioselective benzylic C–O bond cleavage. This regioselectivity turnaround is discussed in terms of major solvent effects affecting the fragmentation paths of a common reaction intermediate. Synthetic applications of these findings led to the synthesis of biologically active compounds, like 2,5-dialkyl-substituted resorcinols, or 1-(3,4,5-trimethoxyphenyl)-2-arylethanes structurally related to combretastatin.

1. Introduction

The regioselective generation of functionalized organometallic reagents is a topic of current interest in synthetic organic chemistry.[1]

Following our interest in the generation of polar organometallic reagents by the reductive cleavage of aromatic[2] and benzylic ethers,[3] as well as the employment of the resulting carbanions in the synthesis of biologically active compounds,[4,5] we investigated the effect of different alkali metals, namely Na and Li, on the reductive metallation of 3,4,5-trimethoxybenzyl methyl ether (**1**).

Indeed, ether **1** can be considered as a cheap starting material allowing either the synthesis of 2,5-dialkylresorcinols, a class of naturally occurring compounds endowed with cytotoxic[6] and antibiotic[7–10] activities, or of 1,2,3-trimethoxyarenes, a class of compounds endowed, inter alia, with interesting anticancer properties.[11]

The key steps of these transformations rely on the set up of highly regioselective procedures, allowing the reductive metallation of ether **1**, either at the aromatic C(4)–O bond, or at the benzylic C–O bond, as depicted in Scheme 1.

Known results on this topic draw attention to the possibility of achieving this goal by an appropriate choice of reaction conditions. Indeed, literature reports show that reductive cleavage reactions of aromatic[12] and benzylic[13] ethers proceed via fragmentation of intermediate radical anions, and point out the importance of counterion and solvent effects on the regioselectivity of the cleavage step.[12–17] Accordingly, besides developing new synthetic applications of the reductive metallation procedure, this work is devoted to highlight the factors governing the regioselectivity of the reductive cleavage reaction under investigation.

2. Results and discussion

2.1. Synthesis of 3,4,5-trimethoxybenzyl methyl ether, 1, and reductive cleavage reactions

3,4,5-Trimethoxybenzyl methyl ether (**1**) was prepared in 88% isolated yield by the reaction of 3,4,5-trimethoxybenzyl alcohol with NaH in dry tetrahydrofuran (THF), followed by reaction of the resulting alkoxide with CH_3I.

Reductive metallations of ether **1** were carried out under Ar, with an excess of Na or Li metal in dry THF, at temperatures ranging from rt to −50 °C. Na chunks and Li wire (0.32 mm) were freshly cut under dry 2,4,4-trimethylpentane (isooctane) immediately before use. Reductive lithiations were run in the presence of 10 (mol %) of naphthalene ($C_{10}H_8$). Selected reactions were quenched with D_2O to provide

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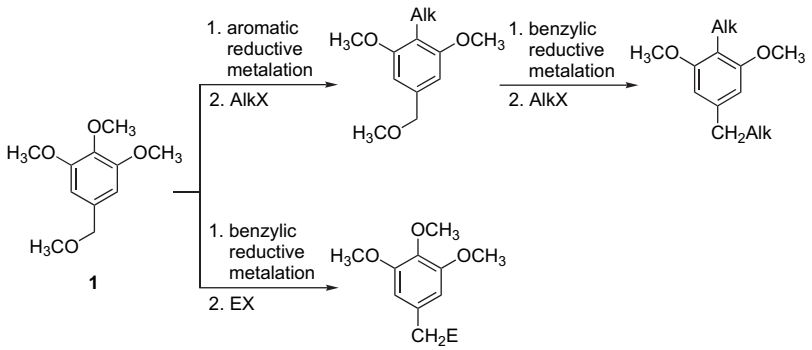
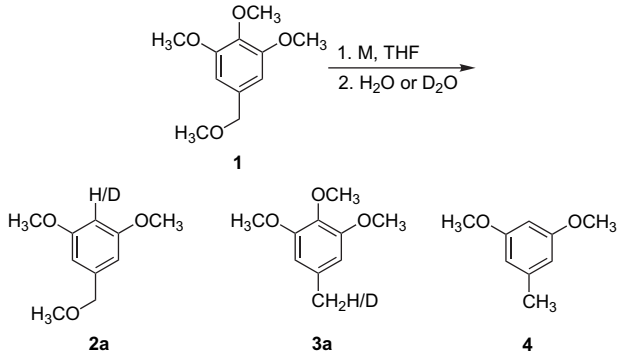


Scheme 1. Reductive metallation routes to 2,5-dialkylresorcinols and 1,2,3-trimethoxyarenes.

evidence for the formation of intermediate organometals (Scheme 2 and Table 1).



Scheme 2. Reductive cleavage of 3,4,5-trimethoxybenzyl methyl ether (**1**). M=Na or Li.

Depending upon the reaction conditions, we recovered reaction mixtures containing different amounts of 3,5-dimethoxybenzyl methyl ether (**2a**), 3,4,5-trimethoxytoluene (**3a**) and 3,5-dimethoxytoluene (**4**). Although reductive metallations of 1,2,3-trimethoxyarenes are usually accompanied by the formation of minor amounts (5–15%) of phenolic compounds,[2] we did not take into consideration the formation of these by-products. It is however worth noting that recovered reaction products always account for more than 90% of the starting material.

Table 1. Reductive cleavage of ether **1**

Entry	Metal (equiv)	T (°C)	t (h)	Product distribution (%)[a]		
				2a (%D)[b]	**3a** (%D)[b]	**4**
1	Na (1.5)	20	16	80[c]	—	—
2	Na (1.5)	0	16	>95 (66)	—	—
3	Na (5.0)	−20	14	>95 (78)	—	—
4	Li (2.5)	0	5	—	78	22
5	Li (2.5)	−20	5	—	85	15
6	Li (2.5)	−50	16	—	>95 (77)	—
7	Na (5)[d]	−20	16	—	>95	<5
8	Li (2.5)[e]	0	12	—	>95	<5

[a] As determined by ^{1}H NMR of crude reaction mixture.
[b] As determined by ^{1}H NMR spectroscopy by monitoring the percentage of deuteration after D_2O quenching.
[c] Alcohol **5** (20%) was also detected.
[d] In the presence of 1 equiv of 15-crown-5.
[e] In the presence of 1 equiv of 12-crown-4.

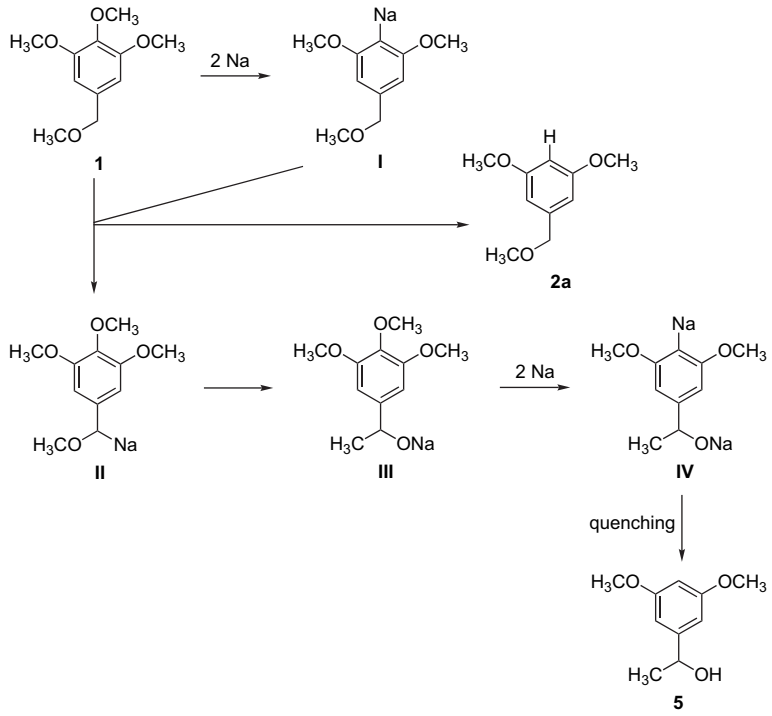
Reduction of ether **1** with 1.5 equiv of Na metal at rt for 16 h, afforded a reaction mixture containing, besides 3,5-dimethoxybenzyl methyl ether (**2a**), minor amounts of 1-(3,5-dimethoxyphenyl)ethanol (**5**) (Table 1, Entry 1).

Formation of this by-product can be rationalized in several ways, all of which, however, require the intermediate formation of (at least) one α-methoxy-substituted benzylic carbanion, as depicted in Scheme 3. Na-mediated reductive metallation of starting material leads to the formation of 2,6-dimethoxy-4-methoxymethylphenyl sodium (**I**), probably undergoing acid–base equilibration with the parent compound, to afford the α-methoxy-substituted benzylic carbanion **II**.

Once benzylic organometal **II** is formed, it undergoes a 1,2-Wittig rearrangement to the corresponding alkoxide **III**.[18] Scheme 3 further describes a likely transformation of intermediate **III** into 1-(3,5-dimethoxyphenyl)ethanol (**5**), via reductive dealkoxylation and protonation. Other possibilities (not reported in Scheme 3) could involve, e.g., acid–base equilibration between ether **2a** and organometallic intermediate **I** (or **IV**) leading to a new α-methoxy-substituted benzylic carbanion.

Lowering the temperature to 0 °C led to exclusive formation of ether **2a**, although a relatively low amount of deuterium was incorporated onto the aromatic ring upon D_2O quenching (Table 1, Entry 2). After several attempts, we obtained a better result by running the reaction at −20 °C in the presence of 5 equiv of Na metal (Table 1, Entry 3). It is worth noting that a reductive metallation run in the presence of a catalytic amount (10 mol %) of naphthalene ($C_{10}H_8$), did not improve this result, nor affect the regioselectivity of the reductive cleavage (not reported in Table 1).

At variance with these results, metallations run in the presence of Li metal (and a catalytic amount of $C_{10}H_8$), led to preferential or exclusive cleavage of the benzylic carbon–oxygen bond. Indeed, reactions run at temperatures ranging from 0 to −20 °C afforded reaction mixtures containing, besides 3,4,5-trimethoxytoluene (**2a**), minor amounts of 3,5-dimethoxytoluene (**4**), i.e., the product of a double dealkoxylation reaction (Table 1, Entries 4 and 5), whilst lowering the reaction temperature to −50 °C allowed the highly regioselective generation of 3,4,5-trimethoxybenzyllithium (Table 1, Entry 6).



Scheme 3. Reductive demethoxylation of ether **1**, and formation of alcohol **5**.

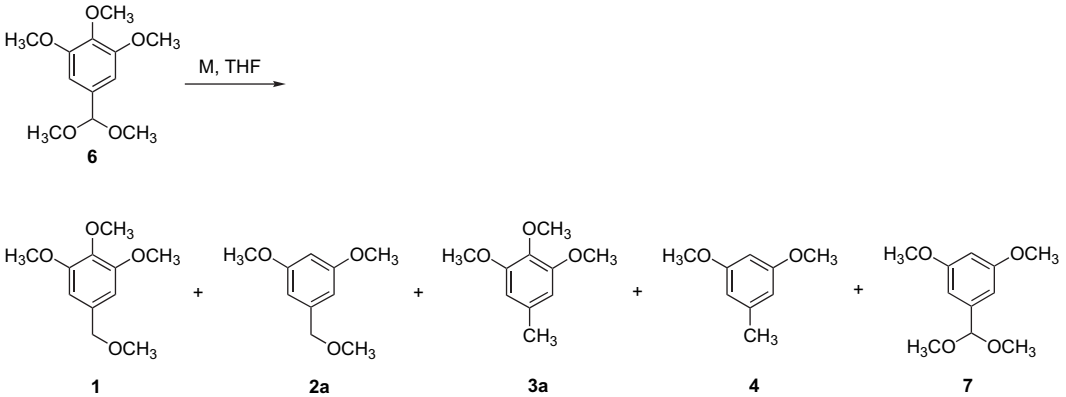
Although the same benzyllithium derivative can be generated by the reductive lithiation of 3,4,5-trimethoxybenzylbromide,[19] it is worth noting that the present methodology presents two distinct benefits. Indeed, our procedure allows the generation of stable solutions of this useful organometal, which can be taken as an advantage from a synthetic point of view (see below), and avoids formation of the corresponding dimeric product, i.e., 1,2-di-(3,4,5-trimethoxyphenyl)-ethane, thus rendering this approach more economical from an atomic point of view.

To rationalize the above observed regioselectivity, we propose that aromatic C–O cleavage of ether **1**, which takes place employing Na as a reducing agent, occurs via poorly solvated or tight ionic pairs, whilst the competitive benzylic C–O cleavage, favoured by the employment of Li metal at relatively low temperatures, preferentially occurs via solvent separated ionic pairs.

To challenge this assumption, ether **1** was reacted with the alkali metals in the presence of crown ethers, i.e., under conditions favouring the formation of solvent separated ionic pairs.[12]

Reduction with Na and 15-crown-5, run at −20 °C, afforded 3,4,5-trimethoxytoluene (**3a**), contaminated by a minor amount (<5%) of compound **4** (Table 1, Entry 7), and an analogous result was obtained employing Li metal and 12-crown-4 at 0 °C (Table 1, Entry 8). A comparison with results obtained in the absence of crown ethers (Table 1, Entries 1–3 for reductions with Na and Table 1, Entries 4–6 for reductions with Li) clearly supports the hypothesis of a major solvent effect on the regioselectivity of the cleavage reaction.

Additional evidence was obtained by running a few reactions on the dimethyl acetal of 3,4,5-trimethoxybenzaldehyde (**6**), a structurally related substrate (Scheme 4 and Table 2). In



Scheme 4. Reductive cleavage of the dimethyl acetal of 3,4,5-trimethoxybenzaldehyde (**6**). M=Na or Li.

Table 2. Reductive cleavage of acetal **6**

Entry	Metal (equiv)	T (°C)	t (h)	Product distribution (%)[a]				
				1	**2a**	**3a**	**4**	**7**
1	Na (1.5)	20	18	—	—	—	—	>95[b]
2	Na (5.0)[c]	−20	18	18	19	—	2	5[d]
3	Li (2.5)	−50	16	22	20	7	3	24[e]

[a] As determined by ^{1}H NMR of crude reaction mixture.
[b] According to Ref. 20.
[c] In the presence of 1 equiv of 15-crown-5.
[d] Compound **6** (56%) was also recovered.
[e] Compound **6** (24%) was also recovered.

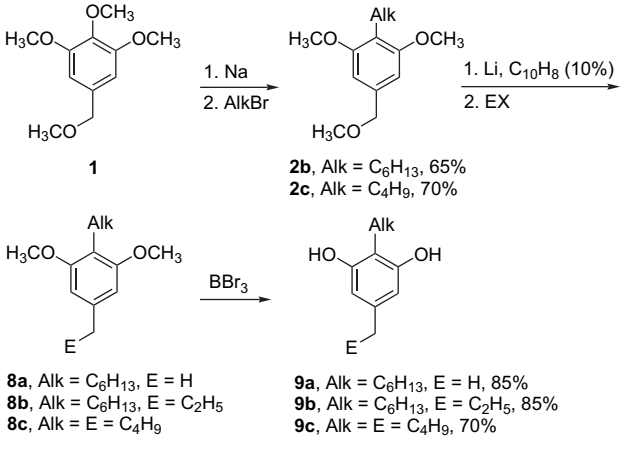
close analogy with ether **1**, reduction of compound **6** with Na metal in THF affords the dimethyl acetal of 3,5-dimethoxybenzaldehyde (**7**) as the only reaction product (Table 2, Entry 1).[20]

Further reductions of **6** were run either with Na metal and 15-crown-5 at −20 °C (Table 2, Entry 2), or with Li metal and a catalytic amount of $C_{10}H_8$ at −50 °C (Table 2, Entry 3).

In these cases, we recovered relatively complex reaction mixtures, due to the fact that benzylic dealkoxylation can occur twice; it is however clear that both reactions led to the formation of major amounts of products of reductive benzylic C–O cleavages, further highlighting that competition between aromatic and benzylic delkoxylation is affected by solvating effects.

2.2. Synthetic applications

2.2.1. Synthesis of 2,5-dialkylresorcinols. We next investigated the reactivity of 2,6-dimethoxy-4-methoxymethylphenylsodium, **I**, towards alkyl halides,[21] with the aim of developing an efficient approach to the synthesis of several biologically active 2,5-dialkylresorcinols, namely 2-hexyl-5-methylresorcinol (**9a**),[22] DB-2073 (**9b**),[8,9] and stemphol (**9c**)[8,9] (Scheme 5).



Scheme 5. Synthesis of 2,5-dialkylresorcinols **9a–c**.

Accordingly, the reaction mixture obtained by the reductive cleavage of ether **1** with Na metal in THF was reacted with an excess of *n*-hexyl bromide, followed by vigourous stirring of the reaction mixture during 22 h, and aqueous work up. According to this procedure, we recovered 1,3-dimethoxy-2-hexyl-5-methoxymethylbenzene (**2b**), in satisfactory isolated yield (65%). The employment of stoichiometric amounts of the electrophile and/or lower reaction times, resulted in significantly lower yields.

Under similar reaction conditions, quenching the intermediate organometal with *n*-BuBr led to the recovery of 1,3-dimethoxy-2-butyl-5-methoxymethylbenzene (**2c**), in 70% isolated yield.

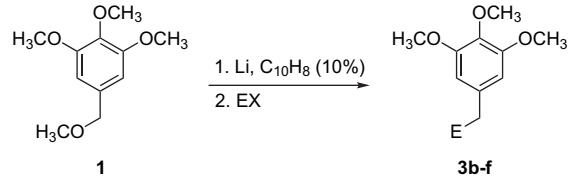
The introduction of an alkyl chain in the benzylic position of ethers **2b** and **2c** was accomplished via a highly regioselective reductive benzylic metallation, run with an excess of Li metal in the presence of a catalytic amount of $C_{10}H_8$. Accordingly, reductive lithiation of *n*-hexyl-derivative **2b**, followed by quenching with H_2O, allowed the almost quantitative recovery of 1,3-dimethoxy-2-hexyl-5-methylbenzene (**8a**). Under similar conditions, quenching of the reduction mixture with ethyl bromide, allowed the recovery of the corresponding alkylated derivative **8b** (90%, as determined by ^{1}H NMR), in satisfactory yield.

Application of a similar procedure to the *n*-butyl-derivative **2c**, followed by quenching with *n*-BuBr, allowed the recovery of 1,3-dimethoxy-2-butyl-5-pentylbenzene (**8c**), in satisfactory yield (82%, as determined by ^{1}H NMR).

Crude dimethyl ethers **8a–c** were not isolated, but directly hydrolyzed to the corresponding resorcinols, by the reaction with BBr_3 in CH_2Cl_2.[23] According to this procedure, resorcinols **9a–c** were recovered in satisfactory overall yields.

2.2.2. Synthesis of combretastatin analogues. Due to the biological significance of several natural products possessing a 1,2,3-trimethoxybenzene ring,[11] we next investigated the reactivity towards electrophilic reagents of the arylmethyllithium obtained by the reductive lithiation of ether **1**, with the aim to synthesize a series of 1-(3,4,5-trimethoxyphenyl)-2-arylethanes, structurally related to biologically active combretastatins.[24]

Accordingly, a new series of reductive lithiations of ether **1** were carried out with an excess of Li wire and in the presence of a catalytic amount of $C_{10}H_8$, at −50 °C, followed by addition of an electrophilic reagent and, finally, aqueous work up (Scheme 6 and Table 3).



Scheme 6. Synthesis of 1-(3,4,5-trimethoxyphenyl)-2-arylethanes **3b–f**. Compound **3b**: E=PhCH$_2$; **3c**: E=4-(CH$_3$O)C$_6$H$_4$CH$_2$; **3d**: E=PhCHOH; **3e**: E=3-(EOMO)-4-(CH$_3$O)C$_6$H$_3$CHOH; **3f**: E=2-(EOMO)-3-(CH$_3$O)-C$_6$H$_3$CHOH; EOM=CH$_3$CH$_2$OCH$_2$O, ethoxymethyl.

Table 3. Reductive lithiation of ether **1**, and reaction with electrophiles[a]

Entry	EX	Product, E	Yield[b] (%)
1	$PhCH_2Cl$	**3b**, $PhCH_2$	73
2	4-$(CH_3O)C_6H_4CH_2Cl$	**3c**, 4-$(CH_3O)C_6H_4CH_2$	50
3	PhCHO	**3d**, PhCHOH	68
4	Ar_1CHO[c]	**3e**, Ar_1CHOH	65
5	Ar_2CHO[d]	**3f**, Ar_2CHOH	61

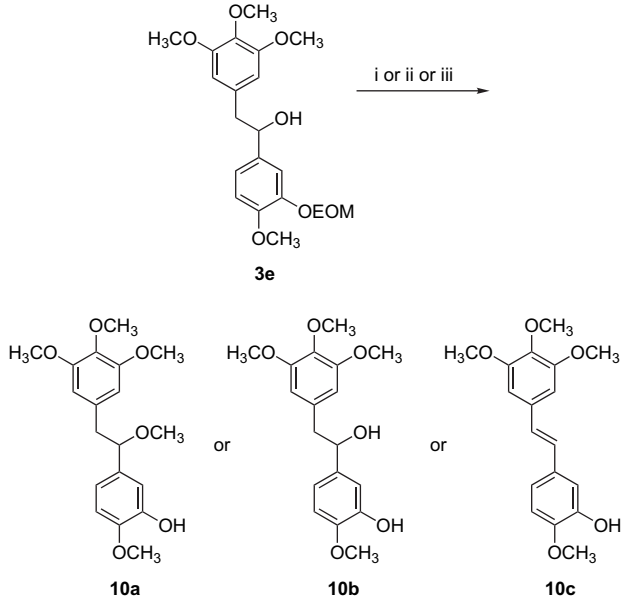
[a] All reactions were run in the presence of 2.5 equiv of Li and 10 mol % of $C_{10}H_8$.
[b] Yields determined on isolated products.
[c] Ar_1=3-(EOMO)-4-$(CH_3O)C_6H_3$.
[d] Ar_2=2-(EOMO)-3-$(CH_3O)C_6H_3$.

Taking advantage of the possibility to generate stable solutions of 3,4,5-trimethoxybenzyllithium, we were able to trap this intermediate with alkyl halides ($PhCH_2Cl$ and 4-$(CH_3O)C_6H_4CH_2Cl$, Table 3, Entries 1 and 2), affording the dibenzyl derivatives **3b** and **3c**, in satisfactory isolated yields.

It is worth noting that 1-(4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethane (**3c**), originally developed as a synthetic analogue of combretastatin A-4, is known to possess cytotoxic activity and to inhibit the polymerization of tubulin.[25]

Good results were obtained trapping the same intermediate with benzaldehydes (PhCHO, 3-(EOMO)-4-$(CH_3O)C_6H_3$-CHO and 2-(EOMO)-3-$(CH_3O)C_6H_3$CHO, Table 3, Entries 3–5), allowing the synthesis of the corresponding alcohols, **3d–f**.

Finally, acidic elaboration of acetal **3e** allowed the synthesis of some natural and synthetic combretastatins, depending upon reaction conditions (Scheme 7).



Scheme 7. Further elaboration of acetal **3e**: (i) 0.6 M HCl in THF/H_2O, 0 °C, 2 h, **10a**, 70%; (ii) 0.6 M HCl in CH_3OH, 0 °C, 2 h, **10b**, 67%; (iii) 2.5 M HCl in dioxane/H_2O, reflux, 1 h, **10c**, 82%.

Indeed, hydrolysis of the starting material with 0.6 M HCl in CH_3OH at 0 °C during 2 h, afforded the methyl ether **10a** in 70% yield. Under similar conditions, but employing THF/H_2O as a solvent, we obtained isocombretastatin A (**10b**), a known inhibitor of the growth of the P388 lymphocytic leukaemia cell line, in 68% isolated yield.[19] Finally, refluxing acetal **3e** with 2.5 M HCl in dioxane/H_2O afforded *trans* alkene **10c** (*trans*-combretastatin A-4) in 82% isolated yield. Although less cytotoxic than its *Z* stereoisomer,[25] this *E* isomer of combretastatin A-4 exhibited significant antibiotic activity.[26]

3. Conclusions

Our results describe the first example of a switch in regioselectivity for the reductive metallation of an aromatic polyether, allowing the generation of different organometallics from a common and easily accessible starting material.

The key step of these protocols is the reductive metallation of different ethereal C–O bonds, and the regioselectivity of this step is efficiently controlled by the choice of reaction conditions, i.e., by taking advantage of the different behaviour of a common intermediate (the π* radical anion) under different reaction conditions.

To rationalize this finding it is necessary to analyze the competitive fragmentation processes of the intermediate π-radical anion, both from a thermodynamic and a kinetic point if view.

According to the literature, dissociating π-radical anions can be divided into two different structural groups, depending on whether the possibility of overlap between the π-network and the σ* of the scissile bond exists (cleavage of a benzylic C–O bond) or not (cleavage of an aromatic C–O bond).[27]

From a thermodynamic point of view, benzylic C–O bond cleavage (with a BDE likely lower than 83–76 kcal/mol) represents the favoured reaction path, in comparison with aromatic C–O bond cleavage (with a BDE of approx. 101–98 kcal/mol).[28,29]

From a kinetic point of view, every fragmentation path requires a certain degree of intramolecular electron-transfer from the π* radical anion to the scissile bond (σ* radical anion), and this electron density redistribution poses intrinsic barriers to the overall fragmentation process.[12,13,27,30–32] However, cleavage of an arylic C–O bond, orthogonal to the π-network, should involve a large intramolecular π*–σ* electron-transfer, as opposed to benzylic C–O bond fragmentation, which appears as an easy reaction, due to possible overlapping between the π* and the σ* systems.[12,27]

Therefore, it appears that benzylic C–O bond fragmentation should be the thermodynamically and kinetically favoured reaction pathway for our intermediate.

To rationalize the result obtained with Na metal, and in agreement with already described ionic pair effects,[12,15–17] we propose that a strong interaction between cation and radical anion, as in a tight ionic pair, strongly affects the electronic distribution of the intermediate and, by lowering the energetic barrier relative to the intramolecular π*–σ*

electron-transfer, makes the aromatic C–O bond cleavage a kinetically favoured reaction path.

Accordingly, our reactions resemble the behaviour observed in the reductive cleavage of alkyl aryl ethers, where competition between aromatic C–O bond versus aliphatic C–O bond cleavage of an intermediate radical anion is driven towards dealkylation (the thermodynamically favoured reaction path) by solvent separated ionic pairs, whilst formation of less solvated or tight ionic pairs favours the dealkoxylation reaction (kinetically controlled reaction path).[12]

Practical application of these findings led to the development of efficient synthetic approaches to different classes of biologically active carboaromatics, thus disclosing a hitherto unexplored regioselectivity feature of reductive metallation reactions.

4. Experimental section

4.1. General

Boiling and melting points are uncorrected; the air bath temperatures on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. Commercially available Li wire (Ø 3.2 mm) was of 99% purity (high Na content), and Na metal (chunks) was of 99% purity. D_2O was of 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with a Varian VXR 300 with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. The resonances of the CH_2D proton is shifted 0.04 ppm (δ) upfield relative to the resonance of the corresponding CH_3 proton; the resonance of the arylmethyl CH_2D carbon appears as a triplet (J=18 Hz) shifted 0.2 ppm (δ) upfield relative to the corresponding arylmethyl CH_3 carbon. IR spectra were recorded with a Jasco FT/IR-480 Plus. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey-Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

4.2. Starting materials

3,4,5-Trimethoxybenzyl methyl ether, **1**, was prepared and characterized according to a literature procedure.[33] 3,4,5-Trimethoxybenzaldehyde dimethyl acetal, **6**, was purchased from Aldrich. Other products were prepared and characterized as follows.

4.3. Preparation of EOM protected benzaldehydes. General procedure

NaH (1.96 g of a 60% dispersion in mineral oil, 49 mmol) was placed under dry N_2 in a 250 mL two-necked flask equipped with reflux condenser and magnetic stirrer, washed with dry THF (3×10 mL), and suspended in dry THF (40 mL). The mixture was chilled to 0 °C and a solution of the appropriate methoxybenzaldehyde (8.6 g, 41 mmol) dissolved in THF (20 mL) was added dropwise. The resulting mixture was stirred for 1.5 h at rt. To this reaction mixture, chilled to 0 °C, a solution of EOMCl (4.6 g, 4.5 mL, 49 mmol), dissolved in 15 mL of THF, was added dropwise. After stirring for 24 h at rt, the mixture was quenched by slow dropwise addition of H_2O (20 mL), and the resulting mixture was extracted with AcOEt (3×20 mL). The organic phase was washed with brine (10 mL), dried (K_2CO_3) and evaporated. Crude products were purified and characterized as follows.

4.3.1. 3-(Ethoxymethoxy)-4-methoxybenzaldehyde. Purified by flash chromatography (AcOEt/petroleum ether/NEt_3=1:1:0.1), pale yellow oil, 53% yield (4.57 g). Found: C, 62.75; H, 6.78. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.71; R_f 0.63 (AcOEt/petroleum ether/NEt_3=1:1:0.1;); IR (liquid film): ν=1686 cm^{-1}; δ_H=1.24 (3H, t, J=7.2 Hz, CH_3CH_2O), 3.78 (2H, q, J=6.9 Hz, OCH_2CH_3), 3.97 (3H, s, OCH_3), 5.34 (2H, s, OCH_2O), 7.01 (1H, d, J=8.4 Hz, ArH), 7.55 (1H, dd, J=1.8, 8.4 Hz, ArH), 7.69 (1H, d, J=1.8 Hz, ArH), 9.86 (1H, s, CHO); δ_C=15.0, 56.1, 64.6, 93.9, 110.9, 115.2, 126.5, 130.0, 147.0, 154.9, 190.8.

4.3.2. 2-(Ethoxymethoxy)-3-methoxybenzaldehyde. Purified by flash chromatography (AcOEt/petroleum ether/NEt_3=3:7:0.1), pale yellow oil, 89% yield (7.67 g). Found: C, 62.73; H, 6.80. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.71; R_f 0.60 (AcOEt/petroleum ether/NEt_3=3:7:0.1); IR (liquid film): ν=1692 cm^{-1}; δ_H=1.22 (3H, t, J=7.2 Hz, CH_3CH_2O), 3.81 (2H, q, J=7.2 Hz, OCH_2CH_3), 3.89 (3H, s, OCH_3), 5.28 (2H, s, OCH_2O), 7.14–7.18 (2H, m, 2×ArH), 7.44 (1H, dd, J=3.6, 6.3 Hz, ArH), 10.46 (1H, s, CHO); δ_C=15.0, 56.10, 65.9, 97.8, 117.7, 119.0, 124.4, 130.4, 149.3, 152.4, 190.5.

4.4. Reduction of 3,4,5-trimethoxybenzyl methyl ether (1), with Na metal, and reaction with electrophiles. General procedure

Two to three pieces of freshly cut Na metal (0.82 g, 5 equiv) were placed under Ar in a 100 mL two-necked flask, equipped with reflux condenser and magnetic stirrer, and suspended in dry THF (10 mL) at −20 °C. 3,4,5-Trimethoxybenzyl methyl ether, **1** (1.50 g, 7.1 mmol), dissolved in dry THF (25 mL), was added dropwise, each metal piece was scratched with a spatula, and the reaction mixture was vigourously stirred at −20 °C for 14 h.

When necessary (Table 1, Entry 7), 15-crown-5 (1.56 g, 7.1 mmol) was dissolved in dry THF and added together with the substrate.

D_2O quenching was performed by dropwise addition of the electrophile (1 mL), dissolved in THF (2 mL), to the reduction mixture chilled at −20 °C. The cold bath was removed, the mixture stirred at rt for several minutes, and finally quenched by slow dropwise addition of H_2O (10 mL) (*caution!*). The mixture was extracted with Et_2O (3×10 mL), the organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent was evaporated.

Quenching with alkyl halides was performed by the dropwise addition of electrophile (5 equiv), dissolved in THF (10 mL), to the reduction mixture chilled at −20 °C. The resulting mixture was vigourously stirred and slowly allowed to reach rt during 22 h, and worked up as described above.

Quenching with $ClCOOCH_3$ (2 equiv) or $HCOOCH_3$ (0.45 equiv) was performed by adding the electrophile dropwise, dissolved in THF (10 mL), to the reduction mixture chilled at −20 °C. The resulting mixture was vigourously stirred at the same temperature during 3 h, and worked up as described above.

Reaction products were purified by flash chromatography. Compounds **2a**,[3] and **5**[34] were characterized by comparison with literature data, other products were characterized as follows.

4.4.1. 1,3-Dimethoxy-2-hexyl-5-methoxymethylbenzene (2b). Purified by flash chromatography (AcOEt/petroleum ether=1:4), colourless oil, 65% yield (1.25 g). Found: C, 71.98; H, 9.96. $C_{16}H_{26}O_3$ requires C, 72.14; H 9.84; R_f 0.54 (AcOEt/petroleum ether=1:4); IR (liquid film): ν=1608, 1589 cm^{-1}; δ_H=0.88 (3H, t, J=6.6 Hz, CH_2CH_3), 1.21–1.48 (8H, m, 4×CH_2), 2.60 (2H, t, J=6.6 Hz, ArCH_2CH_2), 3.40 (3H, s, CH_3OCH_2), 3.81 (6H, s, 2×ArOCH_3), 4.42 (2H, s, ArCH_2O), 6.52 (2H, s, 2×ArH); δ_C=14.1, 22.7, 22.8, 29.2, 29.5, 31.8, 55.7, 58.1, 75.2, 103.1, 119.0, 136.7, 158.2.

4.4.2. 1,3-Dimethoxy-2-butyl-5-methoxymethylbenzene (2c). Purified by flash chromatography (AcOEt/petroleum ether=1:4), colourless oil, 70% yield (1.18 g). Found: C, 70.49; H, 9.38. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30; R_f 0.51 (AcOEt/petroleum ether=1:4); IR (liquid film): ν=1695, 1589 cm^{-1}; δ_H=0.91 (3H, t, J=7.2 Hz, CH_2CH_3), 1.25–1.51 (4H, m, 2×CH_2), 2.61 (2H, t, J=7.2 Hz, ArCH_2CH_2), 3.40 (3H, s, CH_3OCH_2), 3.81 (6H, s, 2×ArOCH_3), 4.42 (2H, s, ArCH_2O), 6.52 (2H, s, 2×ArH); δ_C=14.1, 22.6, 22.8, 31.5, 55.7, 58.1, 75.2, 103.1, 118.8, 136.6, 158.2.

4.4.3. 2,6-Dimethoxy-4-methoxymethylbenzoic acid methyl ester (2d). Purified by flash chromatography (AcOEt/petroleum ether=2:3), colourless oil, 72% yield (1.23 g). Found: C, 59.82; H, 6.78. $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71; R_f 0.41 (AcOEt/petroleum ether=2:3); IR (liquid film): ν=1735 cm^{-1}; δ_H=3.39 (3H, s, CH_3OCH_2), 3.82 (6H, s, 2×ArOCH_3), 3.91 (3H, s, COOCH_3), 4.44 (2H, s, CH_2), 6.54 (2H, s, 2×ArH); δ_C=52.4, 56.0, 58.2, 74.4, 102.7, 142.1, 157.4, 167.0.

4.4.4. Bis-(2,6-dimethoxy-4-methoxymethylphenyl)methanol (2e). Purified by flash chromatography (AcOEt/petroleum ether=7:3), white solid, 55% yield (1.53 g), mp 158–160 °C (EtOH). Found: C, 64.18; H, 7.25. $C_{21}H_{28}O_7$ requires C, 64.27; H, 7.19; R_f 0.42 (AcOEt/petroleum ether=7:3); IR (Nujol): ν=3564, 3525 cm^{-1}; δ_H=3.37 (6H, s, 2×CH_3OCH_2), 3.76 (12H, s, 4×ArOCH_3), 4.39 (4H, s, 2×CH_2), 5.58 (1H, d, J=10.2 Hz, CH), 6.62 (1H, d, J=10.2 Hz, OH), 6.65 (4H, s, 4×ArH); δ_C=55.8, 58.0, 64.3, 74.8, 103.6, 119.5, 138.0, 158.2.

4.5. Reductive metallation of ethers 1, 2b and 2c, with Li metal, and reaction with electrophiles. General procedure

Li (0.21 g, 30 mg atoms, 2.5 equiv) was placed under Ar in a 100 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in dry THF (30 mL). A catalytic amount of $C_{10}H_8$ (80 mg, 0.6 mmol, 10 mol %) was added to the suspended metal. Each metal piece was scratched with a spatula, and the resulting mixture was stirred at rt until a dark green colour appeared. The mixture was chilled at the reported temperature (Tables 1 and 2) and a solution of the appropriate ether (6.0 mmol) dissolved in THF (20 mL) was added dropwise. When necessary (Table 1, Entry 8), 12-crown-4 (1.06 g, 6.0 mmol) was dissolved in dry THF and added together with the substrate.

Reaction mixtures were stirred for the reported time, and a solution of the appropriate electrophile (6.6 mmol, 1.1 equiv), dissolved in THF (10 mL), was added dropwise. After stirring for 20 min, the mixtures were quenched by slow dropwise addition of a 1:1 H_2O/THF mixture (15 mL) (*caution!*), the cold bath removed, and the resulting mixtures extracted with Et_2O (3×10 mL). Organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent evaporated.

Compounds **3a** and **4** were characterized by comparison with commercially available samples. Compounds **3b**[35] and **3c**[25] were characterized by comparison with literature data. Compounds **8a–c** were not purified, but directly submitted to the next reaction step. Other compounds were purified and characterized as follows.

4.5.1. 1-Phenyl-2-(3,4,5-trimethoxyphenyl)ethanol (3d). Purified by flash chromatography (AcOEt/petroleum ether=1:1), pale yellow oil, 68% yield (1.18 g). Found: C, 70.76; H, 7.12. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99; R_f 0.45 (AcOEt/petroleum ether=1:1); IR (liquid film): ν=3464 cm^{-1}; δ_H=2.02 (1H, d, J=3.0 Hz, OH), 2.92 (1H, dd, J=8.1, 13.8 Hz, CH_aH_bAr), 3.00 (1H, dd, J=4.8, 13.5 Hz, CH_bH_aAr), 3.81 (6H, s, 2×ArOCH_3), 3.83 (3H, s, ArOCH_3), 4.87–4.92 (1H, m, ArCHOH), 6.38 (2H, s, 2×ArH), 7.30–7.38 (5H, m, 5×ArH); δ_C=46.4, 56.0, 60.8, 75.1, 106.3, 125.9, 127.6, 128.4, 133.5, 136.5, 143.7, 153.1.

4.5.2. 1-(3-(Ethoxymethoxy)-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanol (3e). Purified by flash chromatography (AcOEt/petroleum ether/NEt_3=5:5:0.1), pale yellow oil, 65% yield (1.53 g). Found: C, 64.35; H, 7.21. $C_{21}H_{28}O_7$ requires C, 64.27; H, 7.19; R_f 0.33 (AcOEt/petroleum ether/NEt_3=5:5:0.1); IR (liquid film): ν=3500 cm^{-1}; δ_H=1.24 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.92 (1H, br s, OH), 2.90–2.95 (2H, m, ArCH_2), 3.76–3.86 (11H, m, 3×ArOCH_3+OCH_2CH_3), 3.88 (3H, s, ArOCH_3), 4.86–4.94 (1H, m, ArCHO), 5.30 (2H, s, OCH_2O), 6.41 (s, 2H, ArH), 6.88 (1H, d, J=8.1 Hz, ArH), 7.00 (1H, dd, J=2.1, 8.4 Hz, ArH), 7.21 (1H, d, J=2.1 Hz, ArH); δ_C=15.0, 46.3, 55.9, 56.0, 60.8, 64.3, 74.8, 94.0, 106.2, 111.4, 114.1, 119.7, 133.7, 136.5, 146.5, 149.1, 153.1.

4.5.3. 1-(2-(Ethoxymethoxy)-3-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanol (3f). Purified by flash chromatography (AcOEt/petroleum ether/NEt_3=5:5:0.1), pale yellow

oil, which solidifies upon standing, 61% yield (1.44 g). Found: C, 64.19; H, 7.11. $C_{21}H_{28}O_7$ requires C, 64.27; H, 7.19; R_f 0.61 (AcOEt/petroleum ether/NEt_3=5:5:0.1); IR (liquid film): ν=3481 cm^{-1}; δ_H=1.24 (3H, t, J=6.9 Hz, CH_3CH_2O), 1.66 (1H, br s, OH), 2.99 (1H, dd, J=13.8, 8.4 Hz, ArCH_aH_b), 3.10 (1H, dd, J=4.8, 13.8 Hz, ArCH_bH_a), 3.79–3.85 (11H, m, 3×ArOCH_3+OCH_2CH_3), 3.86 (3H, s, ArOCH_3), 5.14–5.26 (m, 1H, ArCHO), 6.45 (2H, s, 2×ArH), 6.87 (1H, dd, J=1.8, 8.1 Hz, ArH), 6.99 (1H, dd, J=8.1, 1.8 Hz, ArH), 7.08 (1H, t, J=7.8 Hz, ArH); δ_C=15.1, 44.0, 55.8, 56.0, 60.8, 65.8, 70.4, 97.8, 106.2, 111.4, 118.9, 124.5, 134.5, 136.3, 137.7, 143.4, 151.8, 153.0.

4.6. Hydrolysis of 1,3-dimethoxy-2,5-dialkylbenzenes 8a–c. General procedure

A solution of the 1,3-dimethoxy substituted derivative (5.1 mmol) was dissolved in 80 mL of dry CH_2Cl_2 in a 250 mL two-necked flask, equipped with reflux condenser and magnetic stirrer, under dry N_2. The mixture was chilled to −80 °C, and a 1 M solution of BBr_3 in CH_2Cl_2 (2.2 equiv, 10.4 mL) dissolved in CH_2Cl_2 (20 mL) was added dropwise. The reaction was allowed to warm to rt during 14 h. The mixture was quenched by slow dropwise addition of H_2O (10 mL) (*caution!*), the organic phase separated and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). Organic phases were collected, washed with 1 N HCl (2×10 mL), H_2O (2×10 mL) and brine (2×10 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated.

Crude reaction mixtures were purified by flash chromatography (AcOEt/petroleum ether=1:4). Compounds **9a**,[22] **9b**,[36] and **9c**[10] were characterized by comparison with literature data.

4.7. Synthesis of 5-[1-methoxy-2-(3,4,5-trimethoxyphenyl)ethyl]-2-methoxyphenol (10a)

Acetal **3e** (0.57 g, 1.5 mmol) was added under Ar to a stirred 0.6 M solution of HCl in CH_3OH (15 mL) [obtained by adding AcCl (0.75 mL) to the CH_3OH (15 mL)], chilled to 0 °C. The mixture was stirred at 0 °C until complete disappearance of the starting material (2–3 h), as determined by TLC. The mixture was diluted with H_2O (20 mL), and the solvent evaporated under reduced pressure. The resulting mixture was extracted with AcOEt (4×10 mL), the organic phases were collected, washed with brine (1×20 mL), H_2O (1×20 mL) dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography (AcOEt/petroleum ether=7:3; R_f 0.54) to afford **10a** as a pale yellow oil (0.37 g, 1.1 mmol, 70%), which was characterized as follows.

Purified by flash chromatography (AcOEt/petroleum ether=7:3). Found: C, 65.58; H, 7.11. $C_{19}H_{24}O_6$ requires C, 65.50; H, 6.94; R_f 0.67 (AcOEt/petroleum ether=7:3); IR (liquid film): ν=3418 cm^{-1}; δ_H=2.79 (1H, dd, J=6.0, 13.8 Hz, ArCH_aH_b), 3.03 (1H, dd, J=13.8, 7.5 Hz, ArCH_bH_a), 3.20 (3H, s, CH_3OCH_2), 3.78 (6H, s, 2×ArOCH_3), 3.81 (3H, s, ArOCH_3), 3.89 (3H, s, ArOCH_3), 4.20 (1H, dd, J=6.0, 7.2 Hz, ArCHO), 5.62 (1H, s, OH), 6.31 (2H, s, 2×ArH), 6.68 (1H, dd, J=8.4, 2.1 Hz, ArH), 6.79 (1H, d, J=8.1 Hz, ArH), 6.90 (1H, d, J=1.8 Hz, ArH); δ_C=44.9, 55.9, 56.5, 60.8, 84.6, 106.3, 110.2, 112.8, 118.7, 134.2, 134.8, 145.6, 146.0, 152.7.

4.8. Synthesis of 5-[1-hydroxy-2-(3,4,5-trimethoxyphenyl)ethyl]-2-methoxyphenol (isocombretastatin A, 10b)

Acetal **3e** (0.57 g, 1.5 mmol) was added under Ar to a stirred 0.6 M solution of HCl in 5:1 THF/H_2O (15 mL), chilled to 0 °C. The mixture was stirred at 0 °C until complete disappearance of the starting material (2–3 h), as determined by TLC, then worked up as described for **10a**. The crude product was purified by flash chromatography (AcOEt/petroleum ether/Et_3N=7:3:0.1; R_f 0.54) to afford **10b** as a colourless solid (0.33 g, 1.0 mmol, 67%), which was characterized by comparison with literature data.[19,37]

4.9. Synthesis of (*E*)-1-(3-hydroxy-4-methoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene (*E*-combretastatin A-4, 10c)

Acetal **3e** (0.48 g, 1.2 mmol) was added under Ar to a 2.5 M solution of HCl in 3:1 dioxane/H_2O (12 mL), stirred under reflux during 1 h, and worked up as described for **10a**. The crude product was purified by flash chromatography (AcOEt/petroleum ether/Et_3N=7:3:0.1; R_f 0.67) to afford **10c** as a colourless solid (0.31 g, 1.0 mmol, 82%), which was characterized by comparison with literature data.[38]

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References and notes

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